EGRP Research Highlights

Epidemiology and Genetics Research Program

Web Site: epi.grants.cancer.gov

The Epidemiology and Genetics Research Program (EGRP) supports approximately 400 grants and cooperative agreements annually. Investigators 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. Please visit EGRP's Web site to view a special section with highlights from many other studies: *epi.grants.cancer.gov*.

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Summer 2007

BPC3 Consortium Finds Polymorphisms in the Androgen Receptor Are Not Linked to Breast Cancer Risk


Brian Henderson, M.D.


David Hunter, M.D., Sc.D.


Elio Riboli, M.D., M.Sc.


Michael Thun, M.D.

Androgens may influence breast cancer risk through mechanisms including conversion to estradiol or by binding to the estrogen receptor and/or the androgen receptor (AR) in the breast. The AR is expressed in the normal breast as well as in breast cancer tumors, and both the expression and protein levels have been correlated with tumor invasiveness. To analyze whether polymorphisms in the AR gene are associated with breast cancer risk, **Brian Henderson, M.D., of the University of Southern California/Norris Comprehensive Cancer Center, David Hunter, M.D., Sc.D., of the Harvard School of Public Health, Elio Riboli, M.D., M.Sc., of the Imperial College, London, Michael Thun, M.D., of the American Cancer Society,** and colleagues participating in the EGRP-sponsored Breast and Prostate Cancer Cohort Consortium (BPC3) Study first determined the underlying genetic variation in the AR coding regions in a panel of 95 advanced breast cancer cases and genotyped markers in a panel of 349 healthy women. They identified linkage disequilibrium relationships across the gene and selected haplotype-tagged single nucleotide polymorphisms (htSNPs) that captured the common genetic variants across the locus. The htSNPs then were genotyped in nested breast cancer cases (5,603) and controls (7,480) from the Cancer Prevention Study II, European Prospective Investigation into Cancer and Nutrition, Multiethnic Cohort, Nurses' Health Study, and Women's Health Study cohorts. The authors found no association between any genetic variation in the AR gene and breast cancer risk. They concluded that, in postmenopausal Caucasian women, common polymorphisms in AR are not associated with breast cancer risk.

Cox DG, Blanche H, Pearce CL, Calle EE, Colditz GA, Pike MC, Albanes D, Allen NE, Amiano P, Berglund G, Boeing H, Buring J, Burtt N, Canzian F, Chanock S, Clavel-Chapelon F, Feigelson HS, Freedman M, Haiman CA, Hankinson SE, Henderson BE, Hoover R, Hunter DJ, Kaaks R, Kolonel L, Kraft P, LeMarchand L, Lund E, Palli D, Peeters PH, Riboli E, Stram DO, Thun M, Tjonneland A, Trichopoulos D, Yeager M; Breast and Prostate Cancer Cohort Consortium. A comprehensive analysis of the androgen receptor gene and risk of breast cancer: results from the National Cancer Institute Breast and Prostate Cancer Cohort Consortium (BPC3). Breast Cancer Res. 2006;8(5):R54.

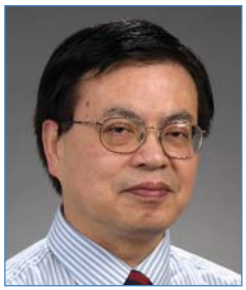
BRCA1 and *BRCA2* Mutations May Be More Frequent Than Previously Thought


Harvey Risch, M.D., Ph.D.

The presence of *BRCA1* and *BRCA2* mutations in the general population and the link between these mutations and various types of cancers have not been well documented. A study by **Harvey A. Risch, M.D., Ph.D., of the Yale University School of Medicine,** and colleagues investigated the presence of *BRCA1* and *BRCA2* mutations in 1,171 unselected patients with newly diagnosed incident ovarian cancer in Ontario, Canada, with respect to cancers reported among their relatives. The patients were screened for germline mutations throughout the *BRCA1* and *BRCA2* genes. Higher risks for various cancers, including ovarian, female breast, and testicular cancer in the general Ontario population, were associated with carrying *BRCA1* mutations versus not carrying mutations (ovarian cancer relative risk (RR) = 21, 95% confidence interval (CI) = 12 to 36; female breast cancer RR = 11, 95% CI = 7.5 to 15; and testicular cancer RR = 17, 95% CI = 1.3 to 230). Similarly, higher risks were associated with carrying *BRCA2* mutations versus not carrying mutations, particularly for ovarian (RR = 7.0, 95% CI = 3.1 to 16), female and male breast (RR = 4.6, 95% CI = 2.7 to 7.8; and RR = 102, 95% CI = 9.9 to 1,050; respectively), and pancreatic (RR = 6.6, 95% CI = 1.9 to 23) cancers. Cancer risks differed according to a mutation's position on the gene. Estimated cumulative incidence to age 80 years among women carrying *BRCA1* mutations was 24 percent for ovarian cancer and 90 percent for breast cancer; in women carrying *BRCA2* mutations, the estimated cumulative incidence was 8.4 percent for ovarian cancer and 41 percent for breast cancer. For the general Ontario population, estimated carrier frequencies of *BRCA1* and *BRCA2* mutations were, respectively, 0.32 percent (95% CI = 0.23% to 0.45%) and 0.69 percent (95% CI = 0.43% to 1.10%). The researchers concluded that *BRCA1* and *BRCA2* mutations may be more frequent in general populations than previously thought and may be associated with various types of cancers. This research was supported by EGRP grants to **Dr. Risch and Steven Narod, M.D., Ph.D., University of Toronto.**

Risch HA, McLaughlin JR, Cole DE, Rosen B, Bradley L, Fan I, Tang J, Li S, Zhang S, Shaw PA, Narod SA. Population BRCAl and BRCA2 mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. J Natl Cancer Inst. 2006 Dec 6;98(23):1694-706.

Human Papillomavirus Type 16 and 18 Variants Show Race-Related Distribution and Persistence



Long Fu Xi, M.D., Ph.D.

Persistent human papillomavirus (HPV) infection, particularly with HPV types 16 or 18, places women at increased risk for cervical cancer. HPV variants, which are viral isolates for any HPV type that differ by less than 2 percent in the L1 gene sequence, appear to segregate geographically. The persistence of these variants in certain geographic populations of infected individuals may be related to the racial composition of that population.

Long Fu Xi, M.D., Ph.D., of the University of Washington, and colleagues studied 1,114 women in the United States participating in the Atypical Squamous Cells of Undetermined Significance/Low-Grade Squamous Intraepithelial Lesion Triage Study who were positive for HPV16 and/or HPV18 at enrollment and classified the HPV variants based on established HPV lineages. They found that 63.9 percent of women infected with HPV18 who self-reported as African American were infected with the HPV18 African variant (95% confidence interval (CI) = 53.5% to 73.4%); 54.2 percent of white women infected with HPV18 were infected with the European variant (95% CI = 46.3% to 61.9%). The likelihood of staying HPV18 positive was statistically significant and higher for African-American women if infected with the African variant compared to the European variant, and statistically significant and higher for white women if infected with the European variant compared to the African variant. The same pattern was found for HPV16 infection. This work suggests that HPV infection persists longer in a host whose race indicates an ancestral geographic distribution that once was shared with that of the infecting HPV variant. This study was funded by an EGRP grant to Dr. Xi.

Xi LF, Kiviat NB, Hildesheim A, Galloway DA, Wheeler CM, Ho J, Koutsky LA. Human papillomavirus type 16 and 18 variants: race-related distribution and persistence. J Natl Cancer Inst. 2006 Aug 2;98(15):1045-52.

Multiple-Type Human Papillomavirus Infection Increases Risk of Cervical Cancer

Helen Trottier, Ph.D.

Human papillomavirus (HPV) infection is one of the most common sexually transmitted diseases and plays the main causal role in cervical carcinogenesis. Certain HPV genotypes, such as HPV16, are associated with a high risk of cervical cancer, but little is known about the effects of infection with multiple HPV genotypes on cervical cancer.

Helen Trottier, Ph.D., and Eduardo Franco, Dr.P.H., of McGill University, and colleagues used PCR to type HPV present in cervical specimens from 2,462 Brazilian women and assessed the relationship between infection with multiple HPV types and any-grade squamous intraepithelial lesions (SIL) and high-grade SIL (HSIL). Infection with multiple HPV types was associated positively with HSIL risk. Relative to women consistently negative for HPV infection, after a 1-year followup for HSIL, women infected with a single type of HPV had an odds ratio (OR) of 41.5, 95% confidence interval (CI) = 5.3 to 323.2; women infected with two to three types of HPV had an OR of 91.7, 95% CI = 11.6 to 728.1; and women infected with four to six types had an OR of 424.0, 95% CI = 31.8 to 5,651.8. The excess risk associated with multiple HPV-type infection persisted after excluding women infected with HPV16 or other high-risk HPV types, or for persistent infections, particularly for any-grade SIL. This work suggests that infection with multiple HPV types may act synergistically in cervical carcinogenesis, or that harboring multiple HPV types may be a marker for a decreased immune response to HPV and thus to greater risk. This research is supported in part by an EGRP grant to Dr. Franco.

Eduardo Franco, Dr.P.H.

Trottier H, Mahmud S, Costa MC, Sobrinho JP, Duarte-Franco E, Rohan TE, Ferenczy A, Villa LL, Franco EL. Human papillomavirus infections with multiple types and risk of cervical neoplasia. Cancer Epidemiol Biomarkers Prev. 2006 Jul;15(7):1274-80.

Colorectal Cancer Risk Associated Jointly With Smoking and NSAID Use

Victoria Chia, Ph.D.

Smoking has been associated with an increased risk of colorectal cancer, and nonsteroidal anti-inflammatory drugs (NSAIDs) have been associated with a reduced risk of colorectal cancer. In a population-based case-control study, **Victoria M. Chia, Ph.D., of the Fred Hutchinson Cancer Research Center and the University of Washington**, and colleagues evaluated the joint association between smoking and regular NSAID use with colorectal cancer risk and examined these associations stratified by tumor microsatellite instability (MSI high/low: MSI-H, MSI-L). They analyzed 1,792 incident colorectal cancer cases and 1,501 population controls in the Seattle area from 1998 to 2002, and assessed MSI in tumors of 1,202 cases. Individuals who had ever smoked had an increased risk of developing colorectal cancer. Individuals who were currently using NSAIDs had a 30% lower risk of developing colorectal cancer compared to non-NSAID users. The data also demonstrated that, relative to current NSAID users who never smoked, individuals who had both smoked for more than 40 years and had never used NSAIDs had the highest risk for colorectal cancer. Compared with nonsmokers, a greater number of tumors in smokers were classified as MSI-H than as MSI-L. NSAID use did not reduce the risk of MSI-H or MSI-L tumors in long-term smokers. Yet smokers who never used NSAIDs had a higher likelihood of having MSI-L tumors. The researchers concluded that there seems to be a synergistic inverse association that implies protection against colorectal cancer overall as a result of NSAID use and nonsmoking, but the risk of MSI-H colorectal cancer remains elevated among smokers even when they have a history of NSAID use. This research was supported in part by an EGRP grant to **John Potter, M.D., Ph.D., of the Fred Hutchinson Cancer Research Center and the University of Washington, and through cooperative agreements with members of the Colon Cancer Family Registry and Principal Investigators.**

Chia VM, Newcomb PA, Bigler J, Morimoto LM, Thibodeau SN, Potter JD. Risk of microsatellite-unstable colorectal cancer is associated jointly with smoking and non-steroidal anti-inflammatory drug use. Cancer Res. 2006 Jul 1;66(13):6877-83.

Model Predicts Germline Mutations and Risk of Cancer in the Lynch Syndrome

Sining Chen, Ph.D.

The Lynch Syndrome (hereditary nonpolyposis colorectal cancer, HNPCC), the most common familial colorectal cancer, can be caused by germline deleterious mutations of DNA mismatch repair (MMR) genes. **Sining Chen, Ph.D., of the Johns Hopkins Bloomberg School of Public Health,** and colleagues developed the MMRpro model to estimate the probability of an individual carrying a deleterious mutation in mismatch repair genes *MLH1, MSH2,* and *MSH6* and developing colorectal or endometrial cancer. The probability is assessed on the basis of a detailed family history of colorectal and endometrial cancer for an individual and his or her first- and second-degree relatives. To validate the MMRpro model, the model's predictions were compared with the results of highly sensitive germline mutation detection techniques for 279 individuals from 226 clinic-based families in the United States, Canada, and Australia (referred between 1993 and 2005). In this independent evaluation, MMRpro provided a concordance index of 0.83 (95% confidence interval (CI) = 0.78 to 0.88) and a ratio of observed-to-predicted cases of 0.94 (95% CI = 0.84 to 1.05), demonstrating that the model is more sensitive and more specific than current clinical guidelines for identifying individuals who may benefit from MMR germline testing. Importantly, this model can be used among individuals for whom tumor samples are not available or whose germline DNA tests find no mutation. Some patients who were in this study belong to EGRP's **Colon Cancer Family Registry** (*epi.grants.cancer.gov/CFR*) an international research infrastructure for investigators interested in conducting population- and clinic-based interdisciplinary studies on the genetic and molecular epidemiology of colon cancer and its behavioral implications.

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Independent Associations of Alcohol Drinking or Tobacco Use With Risk of Head and Neck Cancer

Paolo Boffetta, M.D., M.P.H.

A combination of cigarette smoking and alcohol consumption is implicated in at least 75 percent of head and neck cancers. To understand the mechanism of head and neck carcinogenesis and assess the efficacy of interventions to control these risk factors, an understanding of the independent association of each risk factor with cancer risk is needed. Mia Hashibe, Ph.D., of the International Agency for Research on Cancer (IARC), and colleagues performed a pooled analysis of data from 15 case-control studies of head and neck cancer risk and cigarette smoking or alcohol consumption in the absence of the other risk factor. A total of 10,302 head and neck cancer cases and 15,329 controls were obtained from the International Head and Neck Cancer Epidemiology (INHANCE) Consortium, an international collaboration of research groups conducting large molecular epidemiology studies on head and neck cancer. The researchers found that cigarette smoking in never drinkers was associated with an increased risk of head and neck cancer (OR = 2.13 compared to never smokers). Alcohol consumption in the absence of tobacco use was associated with increased risk only at high frequencies of consumption (OR = 2.04 for 3 or more drinks per day versus never drinking). One-quarter of head and neck cancers in never drinkers were attributable to smoking and 7 percent of cancers in never smokers were attributable to alcohol consumption.

The major strength of the pooled analyses, say the authors, was assembly of a very large series of never users of tobacco and never drinkers among head and neck cancer patients and control subjects, which allowed detailed examination of head and neck cancer risks and exploration of differences in risks by cancer subsite, geographic region, and sex. **Paolo Boffeta, M.D., M.P.H. (pictured), of IARC,** directed this pooled analysis. Establishment of the INHANCE Consortium has allowed generation of large sample sizes for analysis of rare subgroups, such as head and neck cancer patients who are never smokers and/or never drinkers. EGRP is a major facilitator of the INHANCE Consortium and provided funding for this pooled analysis. It also provided grant support for some of the individual epidemiologic studies that contributed to the analysis.

EGRP supports cancer epidemiology consortia in numerous ways, such as through grant support, assistance in identifying partners with similar research interests, advice on policies and processes that have proven successful with other consortia, participation on steering committees, and in evaluating established consortia. Access EGRP's Web site to learn more about its work with consortia (*epi.grants.cancer.gov/Consortia*).

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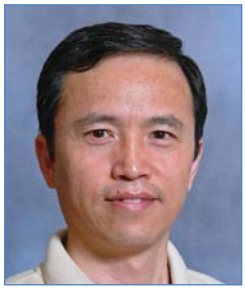
Prediagnostic Level of Serum Retinol Associated With Decreased Risk of Hepatocellular Carcinoma



Jian-Min Yuan, M.D., Ph.D.

Retinol and its derivatives (retinoids) are antioxidants that promote cell differentiation and may protect against the development of hepatocellular carcinoma (HCC) by controlling hepatocellular differentiation and reducing inflammatory responses. Few prospective epidemiologic studies of serum retinol and other antioxidants in relation to HCC risk have been conducted, however. This study by **Jian-Min Yuan, M.D., Ph.D., of the University of Minnesota**, and colleagues examined the relationship between concentrations of antioxidant micronutrients in prediagnostic serum samples and the risk of developing HCC in 213 patients with HCC and 1,087 controls from a cohort of 18,244 men in Shanghai, China, who were monitored from 1986 through 2001. The micronutrients measured included retinol, specific carotenoids, tocopherols, and selenium. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated by quartile (Q) of serum micronutrient concentrations using logistic regression, with adjustments for smoking status, alcohol intake, history of physician-diagnosed hepatitis or liver cirrhosis, and seropositivity for hepatitis B surface antigen (HBsAg). The researchers found that higher prediagnostic serum levels of retinol were associated with a statisti-

cally significant reduced risk of developing HCC in these middle-aged or older Chinese men (Q2 versus Q1, OR= 0.37, CI = 0.22 to 0.61; Q3 versus Q1, OR = 0.30, CI = 0.17 to 0.50; Q4 versus Q1, OR = 0.13, CI = 0.06 to 0.26; $P_{trend} < .001$). The association between serum retinol levels and HCC risk was present in both chronic carriers and noncarriers of the hepatitis B virus. Statistically significant interaction regarding HCC risk between low retinol levels and HBsAg positivity also was found; HBsAg-positive men in the lowest tertile of retinol had a greater than 70-fold higher risk (OR = 72.7, CI = 31.6 to 167.4) of HCC than HBsAg-negative men in the highest tertile of retinol ($P_{interaction} = .018$). Given that HCC is highly fatal, these findings may have implications for clinical practice and prevention efforts. This research was supported by EGRP grants to Dr. Yuan.

Yuan JM, Gao YT, Ong CN, Ross RK, Yu MC. Prediagnostic level of serum retinol in relation to reduced risk of hepatocellular carcinoma. J Natl Cancer Inst. 2006 Apr 5;98(7):482-90.

Newly Published Research on Non-Hodgkin Lymphoma Shows the Power of Consortia

Ten papers on non-Hodgkin lymphoma (NHL) were published in the March 2007 issue of *Cancer Epidemiology, Biomarkers & Prevention*. These papers stem from a symposium focusing on the role of the environment in NHL risk that was held at the April 2006 annual meeting of the InterLymph Consortium. The information presented at the symposium and published in the journal contributes to our understanding of how behavioral and environmental factors, such as infectious agents, sunlight exposure, obesity, and chemical exposure, affect the risk of developing NHL.

InterLymph is an EGRP-sponsored consortium for epidemiologic research on lymphoma. Members have completed or have ongoing case-control studies of lymphoma and participate in collaborative research by undertaking projects that pool data across studies. Consortia like InterLymph facilitate large-scale collaborations that are needed to address complex questions that cannot be answered through the efforts of investigators at a single institution or from a single discipline.

Access EGRP's Web site to learn more about InterLymph (*epi.grants.cancer.gov/InterLymph*) and about the many ways in which EGRP supports consortia (*epi.grants.cancer.gov/Consortia*).

Cancer Epidemiol Biomarkers Prev. 2007 Mar;16(1).

Vitamin D Intake Associated With a Lower Risk for Pancreatic Cancer in Two Cohort Studies


Charles Fuchs, M.D., M.P.H.

Vitamin D and its analogs show strong antitumor effects in a variety of tissues, including the pancreas. A study by Halcyon Skinner, Ph.D., of Northwestern University, and colleagues looked at associations between dietary intake of vitamin D, calcium, and retinol and subsequent risk for pancreatic cancer in two large, EGRP-supported prospective cohort studies: the Health Professionals Follow-up Study, which includes 46,771 men ages 40 to 75 years as of 1986, and the Nurses' Health Study, which includes 75,427 women ages 38 to 65 years as of 1984.

Researchers collected information on Vitamin D dietary intake, documented incident pancreatic cancer through the year 2000, and identified 365 pancreatic cancer cases. Compared with participants in the lowest category of total vitamin D intake (< 150 IU/d), those participants who consumed ≥ 300 IU/d decreased their risk for pancreatic cancer (relative risk = 0.59). Calcium and retinol intakes were found not to be associated with pancreatic cancer risk. The researchers concluded that higher intakes of vitamin D were associated with lower risks for pancreatic cancer in these two U.S. cohorts, suggesting a potential role for vitamin D in the pathogenesis and prevention of pancreatic cancer.

This research was supported in part by EGRP grants to **Walter Willett, M.D., Dr.P.H., and Graham Colditz, M.D., Dr.P.H., both of Harvard University and Brigham and Women's Hospital; and Charles Fuchs, M.D., M.P.H. (pictured), of Harvard University, Brigham and Women's Hospital, and Dana-Farber Cancer Institute.**

Skinner HG, Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Vitamin D intake and the risk for pancreatic cancer in two cohort studies. Cancer Epidemiol Biomarkers Prev. 2006 Sep;15(9):1688-95.

Recent-Onset Diabetes Mellitus May Be an Early Marker for Pancreatic Cancer

Elizabeth Holly, Ph.D., M.P.H.

Diabetes has been hypothesized to be both a risk factor for and a consequence of pancreatic cancer. Patients with diabetes have been shown to have an approximately 2-fold risk of developing pancreatic cancer, and new-onset diabetes may be caused by pancreatic cancer.

Furong Wang, M.D., of the University of California, San Francisco, and colleagues performed a population-based case-control study of pancreatic cancer in the San Francisco Bay area, involving 532 cases with newly diagnosed pancreatic cancer and 1,701 controls. They found that participants with pancreatic cancer were more likely to report a history of diabetes than controls (odds ratio = 1.5, 95% confidence interval (CI) = 1.1 to 2.1). Diabetics in the case group reported a shorter duration of diabetes and a larger proportion of insulin users. Risk for pancreatic cancer decreased as the duration of diabetes increased. There was no association with pancreatic cancer and insulin use for 5 or more years, but insulin use for less than 5 years was associated with a 6.8-fold increased risk for pancreatic cancer (95% CI = 3.7 to 12).

The authors concluded that recent-onset diabetes may be a complication of or an early marker for pancreatic cancer. This research was supported by EGRP grants to **Elizabeth Holly, Ph.D., M.P.H. (pictured), of the University of California, San Francisco, and Stanford University.**

Wang F, Gupta S, Holly EA. Diabetes mellitus and pancreatic cancer in a population-based case-control study in the San Francisco Bay Area, California. Cancer Epidemiol Biomarkers Prev. 2006 Aug;15(8):1458-63.

LTA May Modify the Association Between NSAID Use and Decreased Risk of Advanced Prostate Cancer

Graham Casey, Ph.D.

Studies show that nonsteroidal anti-inflammatory drugs (NSAIDs) have protective effects against prostate cancer, but this may exist only among certain subgroups of men, such as those with particular variants in inflammatory response genes.

Xin Liu, M.D., Ph.D., of the University of California, San Francisco, and colleagues conducted a case-control study (n = 1,012) of the association between NSAID use and more advanced prostate cancer and evaluated whether the association was modified by a functional polymorphism in the lymphotoxin alpha *(LTA)* gene (*LTA* C+80A, where the CC genotype results in higher *LTA* production). The *LTA* protein modulates the immune and inflammatory response to pathogens. The researchers found an inverse association between NSAID use and disease (odds ratio (OR) = 0.67, 95% confidence interval (CI) = 0.52 to 0.87), which was modified by the *LTA* C+80A variant (p for interaction = 0.03).

John Witte, Ph.D.

In men with the CC genotype, the inverse association between NSAID use and prostate cancer was substantially stronger (OR = 0.43, 95% CI = 0.28 to 0.67). NSAID use was not found to be associated with disease for men without the CC genotype (p = 0.30). Similar associations were observed when dose/duration of NSAID use were studied.

These results suggest that prostate cancer chemoprevention by NSAIDs may be most appropriate for men with the *LTA* +80CC genotype. This research was supported by EGRP grants to **Graham Casey, Ph.D., of The Cleveland Clinic Foundation, and John Witte, Ph.D., of the University of California, San Francisco (both pictured).**

Liu X, Plummer SJ, Nock NL, Casey G, Witte JS. Nonsteroidal antiinflammatory drugs and decreased risk of advanced prostate cancer: modification by lymphotoxin alpha. Am J Epidemiol. 2006 Nov 15;164(10):984-9. Epub 2006 Aug 24.

Association Strengthened Between Genetic Variants at 8q24 and Prostate Cancer

Multiple research findings showing a link between genetic variants on chromosome 8 and prostate cancer risk are newly published. These findings build on an association found last year between a variant at 8q24 (rs1447295) and prostate cancer risk. First, the Iceland-based company, deCODE Genetics, demonstrated that individuals with specific polymorphisms at rs1447295 and rs16901979 accounted for about 11 to 13 percent of prostate cancer cases in individuals of European descent and 31 percent of cases in African Americans.

Second, the Cancer Genetics Markers of Susceptibility (CGEMS) initiative validated the original deCODE Genetics finding (rs1447295) and found a third locus at 8q24 (rs6983267) that strongly predicts prostate cancer risk. Independently, this locus may be responsible for up to 20 percent of prostate cancer cases among white men in the United States.

Third, the EGRP-funded Multiethnic Cohort (MEC) Study identified seven genetic variants that independently predict risk for prostate cancer in the locus at 8q24. Most of the seven variants were of highest frequency in African Americans. The high prevalence of these deleterious variants may contribute to the higher rate of prostate cancer among African Americans. Laurence Kolonel, M.D., Ph.D., of the Cancer Research Center of Hawaii, is principal investigator of the MEC Study.

The EGRP-funded Breast and Prostate Cancer Cohort Consortium (BPC3) also confirmed deCODE Genetics findings that variation at rs1447295 is strongly associated with prostate cancer risk. However, the researchers found no association between rs1447295 and breast cancer risk. Other research by the BPC3 investigators is described on page 2.

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High-Risk Melanoma Susceptibility Genes and Pancreatic Cancer, Neural System Tumors, and Uveal Melanoma Across GenoMEL

Alisa Goldstein, Ph.D.

David Elder, M.B., Ch.B.

The Melanoma Genetics Consortium (GenoMEL) is an international consortium of familial melanoma research groups from North America, Europe, Asia, and Australia. This study, by **Alisa Goldstein, Ph.D., of the National Cancer Institute, David Elder, M.B., Ch.B., of the University of Pennsylvania, Julia Newton Bishop, M.D., of the University of Leeds, UK,** and colleagues used the largest familial melanoma sample currently available, taken from across 17 GenoMEL centers, to assess the high-risk melanoma susceptibility genes *CDKN2A/alternative reading frames* (*ARF,* which encodes *p16* and *p14ARF*) and *CDK4,* and their relationship with pancreatic cancer, neural system tumors, and uveal melanoma.

The study included 2,137 cutaneous malignant melanoma patients from 466 melanoma-prone families with at least three melanoma patients per family. Forty-one percent ($n = 190$) of families had mutations in one of three known high-risk melanoma susceptibility genes, most of which involved *p16* ($n = 178$). There were similar frequencies (2–3%) in mutations in *CDK4* ($n = 5$) and *p14ARF* ($n = 7$). The researchers found a strong association between prostate cancer and *CDKN2A* mutations ($P < 0.0001$), which differed by mutation. The group found little evidence of an association between *CDKN2A* mutations and neural system tumors or uveal melanoma and only a marginally significant association between neural system tumors and *ARF* ($P = 0.05$). Researchers also found that the proportion of families with the most frequent founder mutations differed by locale, with similarities between Sweden and the Netherlands; between France, Spain, and Italy; and between the United Kingdom and Australia ($P = 0.0009$).

Julia Newton Bishop, M.D.

This GenoMEL study provides the most extensive characterization to date of mutations in high-risk melanoma susceptibility genes in families with three or more melanoma patients. This research was supported in part by EGRP grants to **Dr. Elder, Lisa Cannon Albright, Ph.D., of the University of Utah, and Nicholas Hayward, Ph.D., of the Queensland Institute of Medical Research.**

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