

# EGRP Research Highlights

## Epidemiology and Genetics Research Program

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The National Cancer Institute's (NCI) Epidemiology and Genetics Research Program (EGRP), in the Division of Cancer Control and Population Sciences (DCCPS), provides opportunities for investigators to conduct population-based research to increase our understanding of cancer etiology and prevention. EGRP is the largest funder of cancer epidemiology grants nationally and worldwide, supporting approximately 400 grants and cooperative agreements annually. The following pages contain summaries of publications featuring research funded in full or in part by EGRP. The featured research was nominated by extramural investigators and selected by EGRP Program Staff based on scientific merit, innovation, and/or potential public health impact. The names of the first authors and of the EGRP-supported Principal Investigators whose grants are credited in the published papers appear in boldface print. Please visit EGRP's Web site to view highlights from many other studies: <http://epi.grants.cancer.gov>.

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## Alcohol Dehydrogenase Genetic Variants Associated With Susceptibility to Upper Aerodigestive Cancers



Mia Hashibe, Ph.D.

Alcohol, a known risk factor for upper aerodigestive cancers, is metabolized by several enzymes, including alcohol dehydrogenase (ADH). The genes in the ADH pathway are important candidate genes for aerodigestive cancers. **Mia Hashibe, Ph.D., of the International Agency for Research on Cancer (IARC)**, and colleagues investigated six *ADH* genetic variants in more

than 3,800 aerodigestive cancer cases and 5,200 controls from three separate studies. Earlier research by the investigators reported an association for *ADH1B* R48H variant rs1229984 in a central European population. In the present study, the investigators examined the effect of this *ADH1B* R48H variant and five other *ADH* variants from the previous central European study, two other European studies, and a Latin American study. All studies were coordinated by IARC and followed a similar protocol.

In the pooled analysis, four variants showed a significant association. Variants rs1229984 (*ADH1B*) and rs1573496 (*ADH7*) were associated most strongly with susceptibility to aerodigestive cancer (odds ratio [OR] for codominant model = 0.59; 95% confidence interval [CI] = 0.5 to 0.69;  $p$  under codominant model =  $8 \times 10^{-10}$  and OR = 0.69; 95% CI = 0.61 to 0.78;  $p = 3 \times 10^{-9}$ ; respectively). Although the effects of these genes appear to be relevant for all aerodigestive tract subsites, they may have a more promi-

nent protective effect in esophageal cancer. Additionally, the effects of both *ADH* genes appear to be dependent on alcohol consumption. Little or no effect on disease risk was observed among never drinkers for rs1229984 (*ADH1B*) and rs1573496 (*ADH7*) (OR = 1.02; 95% CI = 0.66 to 1.56; and OR = 0.88; 95% CI = 0.57 to 1.36; respectively). For those who consumed more than the median level of alcohol intake in each study, the protective effect of rs1229984 (*ADH1B*) more than doubled (OR = 0.42; 95% CI = 0.31 to 0.56;  $p_{\text{trend}} = 0.0002$ ), and for rs1573496 (*ADH7*) a 40 percent decreased risk was observed for heavy drinkers (OR = 0.61; 95% CI = 0.50 to 0.75;  $p_{\text{trend}} = 0.065$ ). The investigators suggest the genetic variants may increase the rate of alcohol metabolism in a manner that lowers exposure, although it is not known whether the variants have a causal role or if the observed associations are secondary to other causal variants.

This research was funded in part by an EGRP grant to **Paul Brennan, Ph.D., of IARC**.

Hashibe M, Curado MP, Oliveira JC, Koifman S, Koifman R, Zaridze D, Shangina O, Wünsch-Filho V, Eluf-Neto J, Levi JE, Matos E, Lagiou P, Lagiou A, Benhamou S, Bouchardy C, Szeszenia-Dabrowska N, Menezes A, Dall'Agnol MM, Merletti F, Richiardi L, Fernandez L, Lence J, Talamini R, Barzan L, Mates D, Mates IN, Kjaerheim K, Macfarlane GJ, Macfarlane TV, Simonato L, Canova C, Holcátová I, Agudo A, Castellsagué X, Lowry R, Janout V, Kollarova H, Conway DI, McKinney PA, Znaor A, Fabianova E, Bencko V, Lissowska J, Chabrier A, Hung RJ, Gaborieau V, Boffetta P, Brennan P. Multiple ADH genes are associated with upper aerodigestive cancers. *Nat Genet.* 2008 Jun;40(6):707-9.

## Susceptibility Loci Associated With Distinct Breast Cancer Tumor Characteristics



Montserrat Garcia-Closas, M.D., Dr.P.H.

Breast cancers vary in clinical behavior, appearance, and molecular alterations. Epidemiologic data suggest that different types of breast cancers are associated with different risk factors, have different clinical and prognostic characteristics, and might arise from different etiologic pathways.

**Montserrat Garcia-Closas, M.D., Dr.P.H., of NCI's Division of Cancer Epidemiology and Genetics**, and colleagues used polytomous logistic regres-

sion to measure associations between genotype and risk of breast cancer subtype in 23,039 invasive breast cancer cases and 26,273 controls. Cases and controls of European or Asian origin were obtained from 20 studies in Europe, North America, Southeast Asia, and Australia. Data on survival after diagnosis also were evaluated in 13,527 cases from 13 studies in which most participants were of European origin. Single nucleotide polymorphisms (SNPs) were correlated with seven tumor characteristics (estrogen receptor [ER] and progesterone receptor [PR] status, grade, nodes, size, histology, and stage at diagnosis) and survival after diagnosis. The SNP rs2981582 in fibroblast growth factor receptor 2 (*FGFR2*) was more strongly related

to ER-positive tumors than ER-negative tumors ( $p = 10^{-13}$ ), with lower grade tumors compared to high-grade tumors ( $p = 10^{-8}$ ), and with node-positive tumors compared to node-negative tumors ( $p = 0.013$ ). Because the causative variant is likely to be one of six variants in rs2981582 located in a region of intron 2 that contains multiple transcription factor binding sites, its association with breast cancer risk may be mediated through differential levels of *FGFR2* expression, and risk may be stronger and more clinically relevant for the subset of tumors that express high levels of the receptor. The association for rs13281651 in 8q24 also was stronger for ER-positive, PR-positive, and low-grade tumors ( $p = 0.001$ ). Survival was not significantly influenced by the loci after accounting for known prognostic factors.

This evidence suggests that common genetic variants influence the pathological subtype of breast cancer and supports the hypothesis that ER-positive and ER-negative diseases are biologically distinct tumors.

This research was funded in part by an EGRP grant to **Fergus J. Couch, Ph.D., of the Mayo Clinic.**

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## Physical Activity Linked to Reduced Risk for Premenopausal Breast Cancer



Sonia Maruti, M.Sc., Sc.D.

Physical activity may lower postmenopausal breast cancer risk, but its role in reducing premenopausal breast cancer remains unclear. In perhaps the first prospective study to collect data for a broad range of etiologically relevant ages and examine the role of activity throughout life, **Sonia S. Maruti, M.Sc., Sc.D., of Fred Hutchinson Cancer Research Center**, and colleagues investigated whether physical activity is associated with a lower incidence of premenopausal breast cancer and, if so, what age period and exercise intensity are most critical.

Starting in 1997, the investigators collected data for 6 years from 64,777 predominantly white premenopausal women ages 33 to 51 enrolled in the Nurses' Health Study II. In 1997, these women reported their leisure-time physical activity for five age periods, beginning at age 12 to current age. During the first year of the study, the investigators also assessed the participants' occupational activity. In 1997 and again in 2001, participants reported the hours per week and intensity of their walking or leisure-time activity in the previous year. Each activity was assigned a metabol-

ic equivalent value (MET) to classify its intensity. During the study, 550 premenopausal women were diagnosed with invasive premenopausal breast cancer.

Age-adjusted and multivariable-adjusted relative risks (RRs) and their 95% CIs were determined using Cox proportional hazards models. Total activity during the participants' lifetime was found to be most strongly associated with a reduced risk of premenopausal breast cancer. Women who engaged in 39 or more MET hours per week of total activity from age 12 onward had a 23 percent lower risk of premenopausal breast cancer (RR = 0.77; 95% CI = 0.64 to 0.93) than the least active women. This level of activity is equivalent to about 3.25 hours per week of running or 13 hours per week of walking. High levels of total activity during the ages of 12 to 22 appeared to be most beneficial.

This research was funded in part by an EGRP grant to **Walter C. Willett, M.D., Dr.P.H., of Harvard University and Brigham and Women's Hospital.**

Maruti SS, Willett WC, Feskanich D, Rosner B, Colditz GA. A prospective study of age-specific physical activity and premenopausal breast cancer. *J Natl Cancer Inst.* 2008 May 21;100(10):728-37.

## Gene Variants Linked to Premenopausal Breast Cancer Risk



Jiali Han, Ph.D.

Premenopausal breast cancer may differ in etiology and degree of inherited predisposition from postmenopausal breast cancer. Most of the genetic variants that contribute to the risk of developing sporadic (not familial) breast cancer, however, are relatively unknown. Reduced DNA repair capacity, which may be due to genetic variation in DNA

repair pathways, has been suggested as a predisposing risk factor for both familial and sporadic breast cancer.

In a nested case-control study within the Nurses' Health Study II, **Jiali Han, Ph.D., of Harvard University and Brigham and Women's Hospital**, and colleagues studied 239 predominantly Caucasian women between the ages of 32 and 52 diagnosed with premenopausal breast cancer, and 477 matched premenopausal controls, to evaluate genetic variation in 60 DNA repair genes in relation to breast cancer risk. The final analysis included 1,050 SNPs.

Altered risk for premenopausal breast cancer was found to be associated with 44 SNPs located in 18 DNA repair genes with  $p < 0.05$ . Two SNPs in the *XPF* gene and two SNPs in the *XRCC3* gene had  $p < 0.01$  ( $R^2 = 0.88$  and  $R^2 = 0.99$ ,

respectively). Increased breast cancer risk was observed in study participants with more hypothesized risk alleles in the nonhomologous end-joining repair of double strand breaks (DSB-NHEJ) pathway (OR per risk allele = 1.37, 95% CI = 1.02 to 1.82;  $p_{\text{trend}} = 0.03$ ). Those with four risk alleles had an OR of 1.69 (95% CI = 1.08 to 2.64) compared to women with two or three risk alleles, and those with five or six risk alleles had an OR of 1.92 (95% CI = 1.02 to 3.60).

These data suggest an additive or synergistic effect of multiple DNA repair variants in the DSB-NHEJ pathway on premenopausal breast cancer risk. This study highlights the importance of using a pathway-based approach to analyze multiple genes and polymorphisms to assess cancer risk.

This research was funded in part by EGRP grants to **Dr. Han, Susan E. Hankinson, Sc.D., and David J. Hunter, Sc.D., also of Harvard University and Brigham and Women's Hospital.**

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Han J, Haiman C, Niu T, Guo Q, Cox DG, Willett WC, Hankinson SE, Hunter DJ. Genetic variation in DNA repair pathway genes and premenopausal breast cancer risk. *Breast Cancer Res Treat.* 2008 Jun 13. [Epub ahead of print]

## HRT Use and Oxidative Stress May Affect Postmenopausal Breast Cancer Risk



Sylvia Quick, Ph.D.

Previous studies have consistently shown an increased risk of breast cancer associated with the use of hormone replacement therapy (HRT). Catalase, a common heme enzyme, catalyzes conversion of hydrogen peroxide to water and molecular oxygen, protecting cells from oxidative stress. Oxidative stress could explain the observed

increase in postmenopausal breast cancer risk associated with HRT.

Using the Western New York Exposures and Breast Cancer case-control study, **Sylvia K. Quick, Ph.D., of the State University of New York (SUNY) at Cortland and formerly of SUNY at Buffalo**, and colleagues investigated associations among HRT, postmenopausal breast cancer risk, and a polymorphism in the promoter region of the *CAT* gene

(rs1001179) that affects transcriptional activity and catalase levels in red blood cells. Few studies have examined the effect of *CAT* genotypes on breast cancer risk, and this was the first study to examine the interaction between *CAT* genotypes and HRT use.

Cases included 616 primarily white women with primary, incident, pathologically confirmed breast cancer. Randomly selected controls ( $n = 1,082$ ) were frequency matched to cases based on age and race. Participants provided blood or oral rinse samples for genotyping and completed questionnaires and interviews regarding demographics, medical history, reproductive history, and family history of the disease. A computer-assisted questionnaire administered by trained interviewers assessed postmenopausal HRT use. For women with breast cancer, estrogen receptor status was obtained from medical records.

Alone, the *CAT* genotype was not associated with breast cancer risk. Ever-use of HRT was associated with an increased risk (OR = 1.39; 95% CI = 1.11 to 1.75), becoming more pronounced among those with the variant CT or TT *CAT* genotype (OR = 1.88; 95% CI = 1.29 to 2.75) than among those with the common CC genotype (OR = 1.15; 95% CI = 0.86 to 1.54). Risk associated with  $\geq 5$  years of HRT use was greater among those with at least one variant T allele (OR = 2.32; 95% CI = 1.50 to 3.59). These findings suggest that the *CAT* genotype modifies the effect

of HRT use on breast cancer risk and that HRT may affect oxidative stress.

This research was funded in part by an EGRP grant to **Jo L. Freudenheim, Ph.D., of SUNY Buffalo.**

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## The Pathways Study Examines Impact of Lifestyle Factors on Breast Cancer Prognosis



Marilyn Kwan, Ph.D.

The Pathways Study is one of the first prospective cohort studies to examine the effects of lifestyle factors on breast cancer prognosis.

**Marilyn L. Kwan, Ph.D., of Kaiser Permanente,** and colleagues are examining the effect of lifestyle factors—such as diet, physical activity, quality of life, and use of complementary and alternative medicine

(CAM)—and molecular factors—such as genetic polymorphisms involved in metabolism of chemotherapeutic agents—on cancer recurrence and survival. Study participants are being recruited from the Kaiser Permanente Northern California (KPNC) patient population as soon as possible (typically within 2 months) after receiving a diagnosis of invasive breast cancer.

Recruitment began in 2006; by mid-January 2008, the cohort contained 1,539 women. On enrollment, baseline detailed health and lifestyle questionnaires are administered, anthropometric measurements (arm, waist, hip) are taken, and blood and saliva specimens are collected to enable investigation of other molecular factors. Followup questionnaires and measurements are collected 6 months

and 24 months after baseline to update lifestyle factors and anthropometrics; telephone interviews occur every 12 months after baseline to identify breast cancer outcomes. Information will be abstracted from KPNC's clinical and administrative databases for all cohort members on breast tumor characteristics; chemotherapy, radiation, and hormone therapies; adverse events; medications; laboratory results; clinic visits, hospitalizations, and emergency room visits; comorbidities; and cancer recurrences and new cancers.

During the next several years, the Pathways Study will conduct both descriptive and association analyses and should become a rich resource for examining behavioral and molecular factors and breast cancer prognosis.

This research was funded in part by an EGRP grant to **Lawrence H. Kushi, Sc.D., of Kaiser Permanente.**

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# Strong Evidence of Lung Cancer Susceptibility Locus at 15q25.1



Christopher Amos, Ph.D.

Lung cancer presents a significant public health burden, with more than 1 million cases diagnosed annually. It is the most common cause of cancer deaths worldwide. Two teams of investigators completed genome-wide association studies (GWAS) and independently uncovered an important genetic region that is associated with lung cancer risk.

**Christopher I. Amos, Ph.D., of the University of Texas M.D. Anderson Cancer Center**, and colleagues performed a GWAS of histologically confirmed non-small cell lung cancer to identify common low-penetrance alleles influencing lung cancer risk. The researchers identified 10 SNPs that were significantly associated with susceptibility to lung cancer in 1,154 lung cancer cases and 1,137 controls of European ancestry. They replicated these in two case-control datasets with 711 cases and 632 controls from Texas and 2,013 cases and 3,062 controls from the United Kingdom. Elevated risk for lung cancer was validated for two of the SNPs, rs8034191 and rs1051730, both of which mapped to chromosome 15. The p-values were  $3.15 \times 10^{-18}$  and  $7.00 \times 10^{-18}$ , respectively. The combined adjusted OR for lung cancer associated with both SNPs was 1.32. The genetic variants that may influence lung cancer risk were present in about one-half of the people studied by Amos et al.



Rayjean Hung, Ph.D.

**Rayjean J. Hung, Ph.D., formerly of IARC and the University of California at Berkeley, James D. McKay, Ph.D., also of IARC**, and colleagues led the largest genetic study of lung cancer ever conducted, involving more than 10,000 people from 18 countries, about one-half of whom had lung cancer. The researchers compared 310,023 SNPs between 1,926 cases of primary lung

cancer and 2,522 controls. They also identified the same two SNPs on chromosome 15q25, rs8034191 and rs1051730, as having a strong association with lung cancer ( $p = 9 \times 10^{-10}$  and  $p = 5 \times 10^{-9}$ , respectively). The OR for



James McKay, Ph.D.

carrying one copy of the most significant marker (rs8034191) was 1.27 and for carrying two copies of the allele was 1.80. The findings were replicated in five independent lung cancer studies, comprising 2,513 more cases and 4,752 more controls. After pooling across studies, the ORs were 1.21 and 1.77 for heterozygous and homozygous

carriers, respectively.

The small genomic region containing the lung cancer risk variants contains several genes that interact with nicotine and other tobacco toxins. These genes are nicotinic acetylcholine receptor genes and are studied widely for their potential involvement in tobacco dependence. Interestingly, the two teams did not find that cancer risk was mediated through nicotine addiction as other research has suggested. Identifying genes that are involved in lung cancer may help to identify treatment targets or allow for identification of individuals who are at high risk of disease in combination with smoking or other factors.

This research was funded in part by EGRP grants to **Dr. Amos and Margaret R. Spitz, M.D., M.P.H., University of Texas M.D. Anderson Cancer Center**, and **Paul Brennan, Ph.D., IARC**. Dr. Hung is now on the faculty at the Samuel Lunenfeld Research Institute of Mount Sinai Hospital, Toronto, Canada.

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Ping Yang, M.D., Ph.D.

Chronic obstructive pulmonary disease (COPD) is a recognized risk factor for lung cancer; however, the underlying mechanism for this association is not well defined. COPD includes emphysema and/or chronic bronchitis. It is not clear, however, whether the magnitude of increased lung cancer risk is different when emphysema and chronic bronchitis

occur separately or in combination.

Alpha<sub>1</sub>-antitrypsin deficiency ( $\alpha_1$ ATD) is one of the most common genetic disorders in the U.S. population and can result in early onset emphysema in homozygous individuals.  $\alpha_1$ ATD carriers (i.e., heterozygous individuals) do not normally have severe  $\alpha_1$ ATD-related diseases and may not be aware of their carrier status, but they may be more vulnerable to tobacco smoke exposure than noncarriers. **Ping Yang, M.D., Ph.D., of Mayo Clinic**, and colleagues tested whether  $\alpha_1$ ATD carriers are predisposed to a higher risk for lung cancer, adjusting for the effects of tobacco smoke exposure and COPD.

The case-control study, which represented a U.S. midwestern population in and around Minnesota, included 1,856 patients with incident lung cancer, 1,585 community residents, and a second control group of 902 full siblings of the patients. Using structured interviews, self-administered questionnaires, and medical records, the investigators collected a complete family history regarding cancer, other lung disease, and tobacco smoke exposure. Patients' med-

ical records also provided data about alcohol use, lung cancer histologic findings, staging, anatomic location and treatment, and other medical conditions. Conditional logistic regression models were used to examine the effects of tobacco exposure history, history of chronic lung diseases (emphysema only, chronic bronchitis only, or both), and  $\alpha_1$ ATD status on lung cancer risk. In the comparison between cases and community controls, the investigators observed that  $\alpha_1$ ATD carriers had a 70 percent higher risk of developing lung cancer than noncarriers (OR = 1.7; 95% CI = 1.2 to 2.4). When patients with lung cancer were compared with their cancer-free siblings, lung cancer risk doubled in  $\alpha_1$ ATD carriers (OR = 2.0; 95% CI = 1.4 to 2.7). This study suggests the estimated attributable risk (EAR) for  $\alpha_1$ ATD carriers, COPD, and exposure to tobacco smoke among never smokers was 12 percent, 10 percent, and 41 percent, respectively. After adjusting for pack-years of cigarettes smoked, the EAR among heavy smokers who are  $\alpha_1$ ATD carriers was 11 percent and for COPD was 12 percent. Less than 10 percent of the population are  $\alpha_1$ ATD carriers; however, the relative and attributable risk is among the highest for gene effects on the risk of a common cancer.

This research was funded in part by an EGRP grant to Dr. Yang.

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Yang P, Sun Z, Krowka MJ, Aubry MC, Bamlet WR, Wampfler JA, Thibodeau SN, Katzmann JA, Allen MS, Midthun DE, Marks RS, de Andrade M. Alpha<sub>1</sub>-antitrypsin deficiency carriers, tobacco smoke, chronic obstructive pulmonary disease, and lung cancer risk. *Arch Intern Med.* 2008 May 26;168(10):1097-103.



Ilir Agalliu, M.D., Sc.D.

Statins, commonly used drugs in the United States for the treatment of high cholesterol, have been of interest in relation to prostate cancer etiology because cholesterol is a precursor of androgens that influence cell signaling pathways. Additionally, in experimental models, statins have been shown to inhibit cell proliferation, inflammation, oxidative stress, angiogenesis, and metastasis. However, previous studies of the association between statin use and prostate cancer risk have been inconclusive.

**Ilir Agalliu, M.D., Sc.D., of Albert Einstein College of Medicine and formerly of Fred Hutchinson Cancer Center**, and colleagues conducted a population-based case-control study in King County, WA, to study the potential relationship between statin use and prostate cancer risk in Caucasian and African-American men aged 35 to 74. The investigators identified and interviewed 1,001 men with histologically confirmed adenocarcinoma diagnosed between 2002 and 2005 through the Seattle-Puget Sound Surveillance, Epidemiology, and End Results (SEER) cancer registry; 942 age-matched controls without a history of prostate cancer were identified by random-digit dialing. Information about demographics, lifestyle, and medical history, including prostate cancer screening history, statin use based on ever use, type of statin used, dates of first and last use, and total duration of use for each episode was collected from cases and controls. The cancer registry provided information on Gleason score, tumor stage, and serum prostate-specific antigen (PSA) level at diagnosis for cases. The investigators also genotyped variants in two cytochrome P-450 (CYP) genes that affect statin metabolism: *CYP3A4* (rs2740574) and *CYP3A5* (rs776746).

ORs and 95% CIs were calculated using unconditional logistic regression. Covariates included in the model were

age, race, and prostate cancer screening history. Additional adjustments included family history of prostate cancer, smoking status, body mass index (BMI), alcohol consumption, income, education, and physical activity. Statin use prevalence was similar in cases and controls (OR = 0.98, 95% CI = 0.80 to 1.21). No associations were found between statin use and clinical features of prostate cancer such as Gleason score, tumor stage, or prostate cancer aggressiveness status. Similarly, the investigators found no significant differences in risk estimates when analyses were stratified by age, race, first-degree family history of prostate cancer, use of nonsteroidal anti-inflammatory drugs, and CYP gene variants.

A statistically significant interaction was observed, however, between BMI and ever use of statin (interaction  $p = 0.03$ ) and duration of use (interaction  $p = 0.04$ ) on risk of prostate cancer. Obese men (BMI  $\geq 30$  kg/m<sup>2</sup>) who reported current statin use showed an increased risk (OR = 1.5, 95% CI = 1.0 to 2.24) relative to obese nonusers, with a stronger association observed in obese men who used statins for 5 years or more (OR = 1.80, 95% CI = 1.06 to 3.03). In view of the high prevalence of statin use and obesity within the U.S. population, these observations warrant further investigation because those with higher BMIs are more likely to have comorbid conditions that also may be associated with altered hormone levels that could influence prostate cancer risk.

This research was funded by an EGRP grant to **Janet L. Stanford, Ph.D., of the Fred Hutchinson Cancer Research Center and School of Public Health and Community Medicine, University of Washington.**

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Agalliu A, Salinas CA, Hansten PD, Ostrander EA, Stanford JL. Statin use and risk of prostate cancer: results from a population-based epidemiologic study. *Am J Epidemiol.* 2008 Aug 1;168(3):250-60.

# HHV-8 Incidence and HIV-1 Infection in Early Childhood in Zambia



Veenu Minhas, Ph.D.

Human herpesvirus 8 (HHV-8) is the infectious agent that causes Kaposi's sarcoma; in Zambia, the incidence of Kaposi's sarcoma in children increased significantly with the emergence of the human immunodeficiency virus type 1 (HIV-1) epidemic. Zambian children are thought to contract HHV-8 infection early in life, but the extent and route of HHV-8 infection and

whether HIV-1 infection is a risk factor remain unclear.

In a prospective, longitudinal cohort study of 1,424 mother-infant pairs in Lusaka, Zambia, **Veenu Minhas, Ph.D., of the Nebraska Center for Virology and School of Biological Sciences, University of Nebraska**, and colleagues evaluated the annual incidence of HHV-8 from birth through 48 months of age and assessed whether maternal and pediatric HIV-1 infections were a risk factor for HHV-8 infection. The study provided the first documentation of annual HHV-8 incidence rates in early childhood in an African endemic area.

Mothers were divided into four groups at delivery based on seropositivity for HIV-1 and/or HHV-8. Mothers were encouraged to return with their children for followup, and children were followed for evaluation of both HHV-8 and

HIV-1 seropositivity between 12 and 48 months of age. Based on 1,532 total child-years of followup, the incidence rate of HHV-8 seroconversion was 13.8 infections per 100 child-years over 48 months. Fluctuations in detectable antibody titers were observed during the course of the study; therefore, the true rates of HHV-8 infection may be underestimated.

HIV-1 infection in the child was found to be the strongest risk factor for HHV-8 seroconversion (adjusted hazard ratio = 4.60, 95% CI = 2.93 to 7.22), although it is not known whether this is due to the children having higher exposure to HHV-8, a greater likelihood of infection when exposed to HHV-8, or higher antibody detection when infected. HHV-8 seroconversion was not influenced significantly by maternal HHV-8 or HIV-1 status. The authors suggest that horizontal transmission through saliva may be the major route of HHV-8 infection in early childhood.

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Minhas V, Crabtree KL, Chao A, M'soka TJ, Kankasa C, Bulterys M, Mitchell CD, Wood C. Early childhood infection by human herpesvirus 8 in Zambia and the role of human immunodeficiency virus type 1 coinfection in a highly endemic area. *Am J Epidemiol.* 2008 Aug 1;168(3):311-20.

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- ▶ **Everything you wanted to know about the NCI Grants Process...but were afraid to ask (2005).**  
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