205 **RISK FACTORS FOR DEVELOPMENT OF CERVICAL CANCER IN VENEZUELA AND THE U.S.** Sierra-Torres CH[1], Robazetti SC[2], Arrastia CD[2], Tyring SK[3], Au WW[1]. [1]Preventive Medicine & Community Health Department, UTMB, Galveston, TX 77555. [2]Obstetrics & Gynecology Department, UTMB, Galveston, TX 77555. [3]Microbiology and Immunology Department, UTMB, Galveston, TX 77555.

Cervical Cancer (CC) accounts for 15,700 new cases and 4,900 deaths in the US each year. Epidemiological and clinical data indicate that high-risk human papilloma virus (HPV) play a major role in the etiology of CC. However, most infected women don't develop cancer. Therefore, other cofactors such as immune system functioning, smoking, and sexual behavior may work with HPV to promote for CC. These susceptibility factors can be further influenced by ethnic differences that might account for the significantly high incidence of CC among Hispanics, especially in Latin America, compared to Caucasians. We have initiated a molecular epidemiology study to assess the role of various risk factors for development of CC in women from the US and Venezuela. After being interviewed, women undergo a gynecologic examination with collection of exfoliated cells for a Papanicolaou smear and high-risk HPV DNA detection. In addition, blood specimens are collected to extract genomic DNA for genotyping by PCR methods. Controls are matched for age and place of recruitment. At this stage, there are 46 cases and 82 controls in the Venezuelan population (38±12 years old). There are 60 cases and 16 controls in the US population (38±14 years old) with a Caucasian/Hispanic ratio of 1.5:1.0. Percentage of smokers by ethnicity is 71% for Caucasians, 29% for US-Hispanics and 26% for Venezuelan-Hispanics. Preliminary analysis shows that high-risk HPV infection rate is 66% in the Venezuelan cases compared to the reported 85% in the US. Ongoing analyses include HLA, GTSM1-T1, & CYP2E1 genotyping for susceptibility to HPV infection and cigarette mutagens (to be presented). Our study should provide a unique opportunity to elucidate the differential contribution of risk factors for CC. COLCIENCIAS-FULBRIGHT-LASPAU supports CHST.

206 **EFFECTS ON CULTURED MAMMALIAN CELLS OF P,P'-DDE AT RELEVANT ENVIRONMENTAL CONCENTRATIONS.** Simonetti JP[1], Berner J[2], Williams KJ[1]. [1]Biomedical Program, University of Alaska Anchorage, Anchorage AK 99508. [2]Office of Community Health, Alaska Native Tribal Health Consortium, Anchorage AK 99508.

Umbilical cord bloods from Inupiat newborns in Barrow, Alaska were analyzed for the presence of environmental contaminants. One hundred percent of the samples contained measurable levels of p,p'-DDE (1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene). This study was undertaken to ascertain if exposure to p,p'-DDE at the measured concentrations had detectable effects on NIH 3T3 (mouse embryonic) and WS1 (human fetal) cells in culture. Exponentially growing cells were exposed to p,p'-DDE at 1X or 10X the average cord blood concentration. Initial experiments demonstrated that, within hours of exposure to p,p'-DDE, a significant decrease in numbers of both cell types occurred. Subsequent analysis revealed that the decrease in number of NIH 3T3 cells was due to cell death, cumulating in decreased long term cell survival. In contrast, the decrease in WS1 cell number was due to a short recoverable arrest in the cell cycle and had no effect on long-term cell survival. We next examined the effect of p,p'-DDE on the ability of these cells to repair mismatches at a hotspot within the H-*ras* oncogene. Using techniques established previously, we produced a site-specific G/T or G/A mismatch within codon 12 and introduced each mismatch into both cell types with or without cellular exposure to p,p'-DDE. Current results indicate that exposure to p,p'-DDE results in a decrease in the overall ability of WS1 cells to repair mismatches (~8% unrepaired), but no increase in incorrect repair leading to mutations. In contrast, NIH 3T3 cells exposed to p,p'-DDE exhibit an increase in the amount of G/A mismatch incorrectly repaired to T/A (13%), as compared to untreated controls (0%). Overall, this study indicates that p,p'-DDE, at relevant environmental concentrations, does have significant effects on mammalian cells.

207 **EFFECTS OF AGE ON STRUCTURAL CHROMOSOMAL ABNORMALITIES IN SPERM FROM HEALTHY MEN.** Sloter E[1,2], Eskenazi B[3], Kidd S[3], Moore II D[4], Hill F[1], Nath J[2], Wyrobek AJ[1]. [1]Biology and Biotechnology Research Program, Lawrence Livermore National Laboratory, Livermore, CA 94550. [2]Genetics and Developmental Biology Program, West Virginia University, Morgantown, WV 26506. [3]School of Public Health, University of California, Berkeley, CA 94720. [4]California Pacific Medical Center, San Francisco, CA 94115.

The majority of *de novo* structural chromosomal abnormalities in offspring are paternally derived, yet there is little information on their etiology. A study was conducted of the effects of age on the frequencies of structural abnormalities in sperm of healthy non-smoking men aged 22-80y with no current history of reproductive problems or known exposure to genotoxic agents. We applied the recently developed multicolor sperm ACM FISH method (Sloter et al. 2000) to simultaneously detect (a) partial chromosomal duplications and deletions of 1p or 1cen, which are the sperm products of premeiotic or meiotic breakage events or rearrangements, (b) chromosomal breaks within 1cen-1q12, and (c) extra or missing copies of chromosome 1. Structural defects accounted for ~70% of the chromosomal abnormalities detected in ~255,000 total sperm evaluated by the ACM assay. In men 22-28y of age (mean=25y, N=10), the frequency of partial chromosomal duplications and deletions was 8.3±2.2 per 10^4 sperm. On average, partial duplications and deletions were ~2-fold higher (16.1±1.0 per 10^4, P=.003) in men age 65-80y (mean=70y, N=10). Chromosomal breaks within the 1cen-1q12 region were also more prevalent in sperm from these older men (20.8±2.2 versus 11.2±1.8, P=.006). No age effect was detected for numerical abnormalities involving chromosome 1 (P=.9). These data suggest that healthy older men carry significantly higher frequencies of structural chromosomal abnormalities in their sperm than healthy young men. Additional analyses are in progress to determine whether other variables such as days abstinence, past smoking, or diet contribute to these results. [This work was performed under the auspices of US DOE by LLNL, contract W-7405-ENG-48, and funding from NIEHS Superfund P4ZES04705 and WVU.]

208 **CHROMOSOME ABERRATIONS, SOMATIC MUTATIONS, AND CANCER RISK: PAST, PRESENT AND FUTURE.** Smith MT[1]. [1]School of Public Health, University of California, Berkeley, CA 94720-7360, USA.

Cancer is an abnormal genetic phenomenon, involving multiple steps of somatic mutation. Genetic damage can occur at the level of the gene (e.g. point mutations and deletions) or the chromosome (e.g. aneuploidy, translocations). During the last two decades, a wide spectrum of biomarkers of genetic damage has been developed to detect early mutational and chromosomal effects of carcinogenic exposure in humans. Historically, biomarkers have tended to measure mutations in surrogate genes (e.g. HPRT and GPA), or use cytogenetics to assess overall changes in chromosome structure and number. These biomarkers have been shown to be associated with a wide range of carcinogenic exposures, but they are not truly biomarkers of early effect as they are not on the causal pathway of disease. Identification of early causal genetic events in cancer has led to the recent development of novel biomarkers of early effect in high-risk populations. These novel biomarkers measure changes frequently observed among cancer patients, including point mutations in genes such as p53 and RAS, altered gene methylation, aneuploidy (chromosome loss or gain), including monosomy 7 and trisomy 8, and specific chromosome rearrangements such as translocations. The application of fluorescence in situ hybridization and real-time PCR to measure these novel biomarkers in selected populations will be discussed. Future technologies will measure >50,000 endpoints on a drop of blood using proteomics and cellomics and identify all genetic polymorphisms related to susceptibility using high-throughput genomics. Application of these biomarkers to study individuals who may be at risk, but who do not yet have cancer will result in improved early detection, as well a better understanding of the risk factors for cancer itself.