up. Plasma was obtained at entry into the trial and before diagnosis of SPTs. At baseline, case patients (138.09 ng/ml, 95% CI: 121.24 ng/ml-154.94 ng/ml) had significantly higher plasma levels of IGF-I than control patients (108.28 ng/ml, 95% CI: 97.40 ng/ml-119.17 ng/ml) ($p<0.001$). The plasma level of IGFBP-3 was also significantly higher in case patients (2929.32 ng/ml, 95% CI: 2635.8 ng/ml-3182.8 ng/ml) than in control patients (2508.51 ng/ml, 95% CI: 2355.4 ng/ml-2661.6 ng/ml) ($p = 0.019$). High plasma levels of IGF-I were associated with an increased risk of SPTs. This association was dose-dependent in both univariate and multivariate analyses with an adjusted odds ratio (OR) for the highest tertile of IGF-I level of 3.67 (95% CI: 1.73-7.80) in logistic regression model without IGFBP-3 and 2.89 (95% CI: 1.26-6.63) with IGFBP-3. High plasma levels of IGFBP-3 were associated with an increased risk of SPT with an OR of 1.95 (95% CI: 1.01-3.78) in logistic regression model without IGF-I. However, after adjusting for IGF-I, the relationship was not significant (OR = 1.45, 95% CI: 0.70- 2.98). Moreover, higher IGF-I/IGFBP-3 molar ratio were associated with increased risk of SPT with an OR of 2.12 (95% CI: 1.05-4.46). This is the first study demonstrating that plasma levels of IGF-I and IGFBP-3 are higher in patients with SPTs than in patients without SPTs. Thus, measuring plasma levels of IGF-I may be useful markers in assessing risk of second tumors in patients successfully treated for their index cancer. *This study was supported by the following grants: CA86390, CA 52051 and CA74880.*

#4528 Genetic susceptibility, smoking and gene-environment interactions in head and neck cancer. Edward S. Peters, Mei Liu, and Karl T. Kelsey. *Harvard School of Public Health, Boston, MA.*

In order to investigate the role that genetic polymorphisms of metabolic enzymes have in the development of squamous cell head and neck cancer we conducted a case-control epidemiologic study in the greater Boston metropolitan region. The glutathione S-transferase (GST) system catalyzes the conjugation of reactive PAH epoxides with glutathione and is an integral step in carcinogen deactivation. The GSTM1 and GSTT1 genes are lacking in approximately 50% and 20% of Caucasians respectively. These homozygous gene deletions have been associated with multiple malignancies, including oral, lung, bladder and cutaneous cancers. We examined the relationship between the established risk factors for head and neck cancer and genetic polymorphisms of GSTM1 and GSTT1 in head and neck cancer etiology. Determination of the GST genotypes was determined by PCR analyses of DNA obtained from blood of 280 cases and 286 population-based controls. Among Caucasians, 41% of controls and 57% of cases were GSTM1 deleted, and 21% of controls and 19% of cases were GSTT1 deleted. The risk associated with heavy smoking (greater than 27 pack years) was differential based on GSTM1 genotype. Among those with the GSTM1 gene present, the risk of head and neck cancer with heavy smoking was 2.7 (95% CI: 1.2, 6.0), and this effect was elevated among those with GSTM1 deleted, OR=3.9 (95% CI 1.9, 7.9). Similarly, for GSTT1, the risk of heavy smoking among those without the gene was higher (OR=5.1, 95% CI 1.3, 20.5) than for those with the gene (OR=3.2, 95% CI 1.8, 5.8) Furthermore, we observed a significant interaction between smoking and the GST genotypes for head and neck cancer risk. The joint effects models indicated that those individuals with both the at-risk genotype and high smoking exposure were at highest risk for head and neck cancer. For GSTM1 the joint risk was 3.1 (95% CI 1.8 - 5.5), and for GSTT1 the risk for both exposure and null genotype was 2.1 (95% CI 1.1 - 4.3). These findings provide further evidence that individuals deficient in either GSTM1 or GSTT1 have increased susceptible to the effects of heavy smoking and are at significantly elevated risk for oral and pharyngeal cancers compared to those individuals with the gene present. Supported by NIH CA78609

#4529 Identification of lung cancer susceptibility/resistance genes. Bao-Zhu Yuan, Kimberly T. Baldwin, Amy M. Jefferson, David Lowry, and Steven H. Reynolds. *National Institute for Occupational Safety and Health, Morgantown, WV.*

Lung cancer is ranked second only to bladder cancer in the proportion of cases thought to be due to occupational exposures. Genetic factors involved in lung carcinogenesis have been implied by several studies. As an approach to better understand the molecular basis between cancer resistance and cancer susceptiblity, we have used analysis of gene expression as a tool to attempt to identify the genes involved in cancer susceptibility/resistance. To identify the genes involved in lung cancer susceptibility/resistance, we carried out a cDNA array analysis, covering 1176 genes, on several mouse lung cancer susceptible (A/J) cell lines and one mouse lung cancer resistant (C57/BL) cell line. Thirteen genes were observed by cDNA array analysis to have lower mRNA expression in the lung cancer resistant cell line but higher expression in all of the lung cancer susceptible cell lines. These results were further confirmed by RT-PCR analysis. Among the identified genes, secreted phosphoprotein 1 (SPP-1), heat shock protein p86, tumor rejection antigen gp96 (TRA-gp96), Growth Regulated Oncogene 1 (GRO1), insulin-like growth factor binding protein 3, and Nedd-5, all exhibited a dramatic difference (> 5-10 fold) in mRNA expression between lung cancer resistant and lung cancer susceptible cells. In a parallel study, DLC-1, a new candidate tumor suppressor gene for human cancers, showed higher expression in the lung cancer resistant C57/BL cell line but decreased expression in lung cancer susceptible A/J cell lines. Preliminary data obtained by in situ hybridization in non-tumor lung tissues dissected from 6-8 week old mice showed that mRNA expression of SPP-1 and TRA-gp96 was found only in the lung stromal cells of the susceptible A/J mice and not in that of the resistant C57/BL mice. RT-PCR detection of mRNA expression in normal lung tissues of both C57/BL and A/J mice showed the GRO1 expressed at a significantly higher level in A/J mice than in C57/BL mice. GRO1 gene was reported to be a chemokine. Its enhanced expression is regulated by activation of NF-kappaB, leading to accelerated tumor growth, angiogenesis and metastasis in vivo. In eight pairs of mouse low and high invasive lung adenocarcinoma cell lines, four showed significantly higher expression of GRO1 gene in high invasive cell lines as compared with their low invasive cell lines. The determination of GRO1 gene and other genes, identified in this study, in the involvement of lung cancer susceptibility is under further investigation.

#R4530 Occupation and lung cancer risk: A population-based study in St. Petersburg, Russia. Andrea Baccarelli, Oleg Khmelnitski, Serguei Gorbanev, Vladimir Tchibissov, Alexei Lomtev, Irina Klimkina, Olga Averkina, and Mustafa Dosemeci. *Division of Cancer Epidemiology and Genetics, NCI, NIH, DHHS, Bethesda, MD, Medical Academy of Postgraduate Educations, St. Petersburg, Russia, Regional Center of Hygiene and Sanitation, St. Petersburg, Russia, and Leningrad Oblast Pathological Bureau, St. Petersburg, Russia.*

Several occupations or occupational exposures have been established or suggested as risk factors for lung cancer. The Leningrad Province, Russia, a heavily industrialized area with a high number of large factories in a variety of industries, provides a unique opportunity to study the association between occupational risk factors and lung cancer. In this area, post-mortem examinations are performed on approximately 95% of the population who died in hospitals in the Province and a detailed lifetime report of individual job history is recorded and coded by the workplace administration using the standard Russian occupational classification system. We conducted a population- and autopsy-based case-control study on 540 lung cancer cases (474 males and 66 females) and 582 non-lung cancer controls (453 males and 129 females) to evaluate the association between occupational history and lung cancer. Controls were frequency matched to cases by age, gender, smoking, and geographical region. We retrieved information on all subjects about multiple chemical exposures and physical hazards in the workplace, as well as about environmental exposures and life-style risk factors. Lung cancer diagnosis was confirmed by pathological examination performed on autopsy specimens. All statistical analyses were adjusted for age, gender, and smoking using logistic regression models. Lung cancer risk was increased in the manufacturing industry (OR=1.5, 95%CI=1.2-1.9), particularly in the wholesale, retail and food (OR=1.7, 95%CI=1.2-1.4), miscellaneous manufacturing (OR=1.4, 95%CI=1.0-1.8), chemical and metal production (OR=1.4, 95%CI=0.9-2.2) and petroleum, gas, coal and peat industry (OR=1.3, 95%CI=0.9-1.9). When we considered specific occupations, we found an increased risk for lung cancer in sanitary engineers (32 cases and 13 controls, OR = 2.2, 95% CI 1.1-4.3), waitresses (6 cases and 1 control, OR=11.1, 95% CI 1.3-97.8) and loaders (59 cases and 33 controls, OR = 2.0, 95% CI 1.2-3.1), particularly those employed in the chemical and metallurgic industry (7 cases and 1 control, OR = 6.8, 95% CI 0.8-57.6). An increased risk was also found for generic workers