

## Evidence of gene-gene interactions in lung carcinogenesis in a large pooled analysis

Paolo Vineis<sup>1</sup>, Sisko Anttila<sup>2</sup>, Simone Benhamou<sup>3</sup>, Monica Spinola<sup>4</sup>, Ari Hirvonen<sup>2</sup>, Chikako Kiyohara<sup>5</sup>, Seymour J. Garte<sup>6</sup>, Riccardo Puntoni<sup>7</sup>, Agneta Rannug<sup>8</sup>, Richard C. Strange<sup>9</sup> and Emanuela Taioli<sup>6</sup>

<sup>1</sup> Università degli Studi di Torino-ITALY and Imperial College, London UK

<sup>2</sup> Finnish Institute of Occupational Health, Helsinki- FINLAND

<sup>3</sup> INSERM U794 06, Evry-FRANCE

<sup>4</sup> Istituto Nazionale Tumori, Department of Experimental Oncology, Milan-ITALY

<sup>5</sup> Kyushu University Graduate School of Medical Sciences-Department of Preventive Medicine, Fukuoka-JAPAN

<sup>6</sup> University of Pittsburgh, Pittsburgh- USA

<sup>7</sup> National Cancer Research Institute, Environmental Epidemiology Unit, Genoa-ITALY

<sup>8</sup> Karolinska Institutet Stockholm-SWEDEN

<sup>9</sup> Keele University Staffordshire- UK

To test the hypothesis of interaction among genetic variants in increasing the individual risk of cancer, we have studied the cumulative effect on lung cancer risk of variants in three metabolic genes, *CYP1A1*, *GSTM1* and *GSTT1*, which are involved in the metabolism of the tobacco smoke constituents and environmental contaminants polycyclic aromatic hydrocarbons, and of other lung carcinogens. We have selected from the Genetic Susceptibility to Environmental Carcinogens (GSEC) pooled analysis all the studies on lung cancer conducted after 1991 in which all variants were available. The data set includes 611 cases and 870 controls. We found a cumulative effect of the combination of the *a priori* "at risk" alleles for these genes (*p* for trend 0.004). The risk of lung cancer was increased with the combination of *CYP1A1*\*2B or *CYP1A1*\*4 alleles and the double deletion of both *GSTM1* and *GSTT1*, up to an odds ratio of 8.25 (95% confidence interval 2.29-29.77) for the combination including *CYP1A1*\*4; among never smokers, the latter combination was associated with an odds ratio of 16.19 (1.90-137). Estimates did not change after adjustment by the number of cigarettes smoked and duration of smoking, were consistent across ethnicities, and were approximately the same for adenocarcinomas and squamous cell carcinomas. These observations from a large pooled analysis strongly suggest the existence of gene-gene interactions in lung carcinogenesis. People with rare combinations of common gene variants have a high risk of cancer and can be assimilated to subjects with highly-penetrant mutations.

**Key Words:** gene-gene interactions • CYP1A1\*2A, \*2B • GSTM1 • GSTT1 • lung cancer • pooled analysis

Received November 18, 2006; revised February 10, 2007; accepted February 11, 2007.