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CHEMOPREVENTION OF SMOKE-RELATED DNA DAMAGE AND CANCER

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DNA damage is an essential step in the pathogenesis of cancer and probably of other chronic degenerative conditions related to cigarette smoke (CS), such as atherosclerosis, cardiomyopathies, etc. Although the major goal of primary prevention is to refrain from smoking, chemoprevention by means of dietary and pharmacological agents provides a complementary preventive strategy. In spite of its overwhelming epidemiological importance, experimental studies evaluating CS as a complex mixture are relatively scanty. We performed studies *in vitro*, in animal models and in humans aimed at evaluating adverse effects of CS and their modulation. *In vitro*, 26 out of 63 chemopreventive agents (41.3%) inhibited the bacterial mutagenicity of CS, with a potency varying over a 250-fold range. Unfortunately, due to the complexity of CS-host interactions, *in vitro* end-points provide limited information. We are trying to develop suitable carcinogenicity models in mice exposed whole-body to CS, also by using p53 mutant mice. In the meantime, during the last 10 years we evaluated modulation of biomarkers by chemopreventive agents and their combinations in a variety of organs, tissues, and isolated cells of CS-exposed rodents. The investigated biomarkers included: biochemical parameters, adducts to proteins, adducts to mitochondrial DNA, adducts to nuclear DNA, oxidative DNA damage, apoptosis, multigene expression, cytogenetic damage, and histopathological alterations. We are also ready to finalize a lifetime follow-up, from perinatal period to ageing, of several end-points in the progeny of mice exposed to CS during pregnancy. In phase II clinical trials, *N*-acetylcysteine significantly attenuated urine mutagenicity in Italian smokers and decreased cytogenetic damage in buccal cells, DNA adducts and 8-OH-dG in pulmonary alveolar macrophages

of Dutch smokers, whereas oltipraz failed to affect urinary mutagenicity in Chinese smokers. The observed interindividual variations prompted us to implement pharmacogenetic studies aimed at evaluating the influence of metabolic polymorphisms on responsiveness to cancer chemopreventive agents. Both in animal models and humans, we started applying cDNA array technology for multigene expression in order to assess both safety and efficacy of chemopreventive agents at the molecular level. In fact, an optimal agent should be able to attenuate alterations of gene expression resulting from exposure to CS, without excessively altering the physiological background *per se.*