GLUTATHIONE-S-TRANSFERASE MU PHENOTYPE AND GENOTYPE IN WORKERS WITH ASBESTOS-RELATED LUNG DISEASE

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While asbestos-related disorders are among the most well-studied occupational diseases, little is known about factors which affect individual susceptibility to these conditions. A considerable recent literature has implicated the production of oxygen-free radicals in the pathogenesis of asbestos-related diseases. Several workers have recently proposed that the ability of asbestos minerals to induce fibrogenic lung disease is mediated by their known ability to catalyze a Fenton-type reaction, producing cytotoxic and genotoxic electrophilic compounds.

Many of these electrophilic products of free radical generation could either interact with Phase I metabolic reactions or be detoxified by Phase II enzymatic conjugation reactions. Hydroxyalkenes, for example, are major products of lipid peroxidation and their efficient detoxification by glutathione-S-transferase is likely essential for normal cellular survival. The induction of significant radical formation by asbestos would, hence, be expected to be accompanied by increased activity of catalyzed conjugation of glutathione to potentially toxic electrophilic compounds like the hydroxyalkenes. To investigate whether the known genetic polymorphism in glutathione-S-transferase mu (GST-1) is associated with susceptibility to the induction of asbestos-related lung disease, we studied 77 workers with either asbestos-related pleural disease, (N=40), asbestosis (N=37), or both. We measured GST-mu activity phenotypically in 48 individuals using tritiated trans-stilbene oxide as a substrate. All of the subjects were genotyped using established PCR-based techniques. There was an excellent correlation between phenotype and genotype with only one discrepancy. The prevalence of GST-1 deleted genotype in individuals with asbestos-related disease was 57%. In controls, the prevalence is 47%. Analysis controlling for duration of exposure and type of asbestos-related disease revealed a non-significant trend toward an over-representation of GST-1 deleted genotype in those with asbestos-induced disease. Smoking, age and other lifestyle factors had no significant effect on this analysis.

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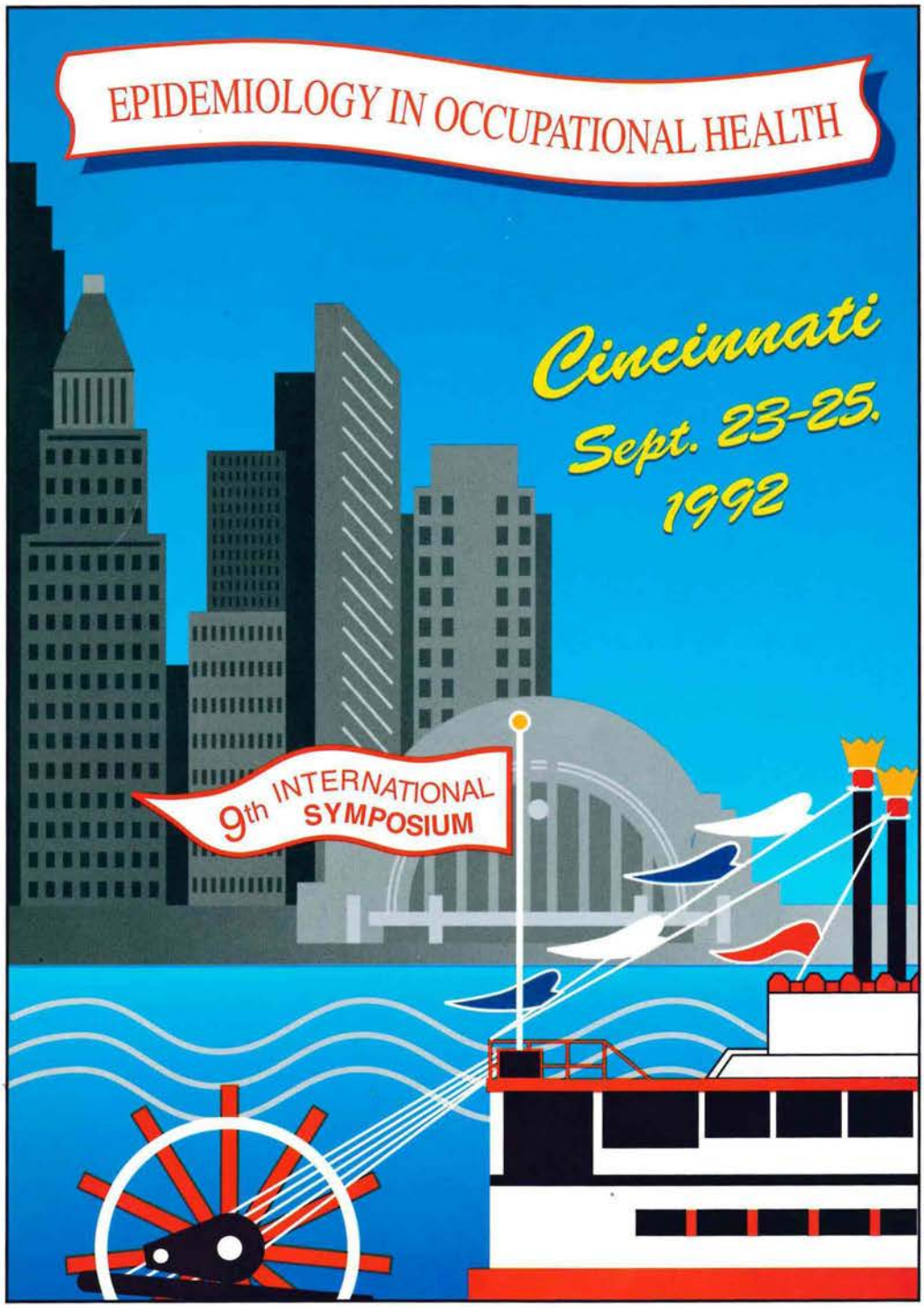

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