ASSOCIATION BETWEEN GLUTATHIONE S-TRANSFERASE T1, M1 AND P1 POLYMORPHISMS AND LUNG FUNCTION IN JAPANESE AND CANADIAN POPULATIONS

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Understanding the environmental and genetic risk factors for lung function decline in the general population is a first step in a prevention strategy against the chronic obstructive pulmonary disease. This study investigated the association between low activity variants in glutathione S-transferase (GST)T1, GSTM1 and GSTP1 gene and lung function in 239 male Japanese participants (54.0 ± 9.9 ys) in a health screening program and 216 male Saskatchewan grain handlers (37.1 ± 9.5 ys). In total Japanese subjects, the mean lung function values did not differ among the GST genotypes. However, current smokers with the GSTM1 null genotype or the GSTT1 present genotype had a lower percent predicted forced expiratory volume in 1 s (FEV1) per forced vital capacity (FVC) than those with the GSTM1 present genotype (90.5 ± 8.2% vs. 94.2 ± 6.6%, P = 0.009) or those with the GSTT1 null genotype (89.4 ± 8.5% vs. 94.0 ± 6.3%, P = 0.02), respectively. In Canadians, the mean lung function values did not differ among GSTM1 and GSTP1 genotypes. However, the subjects with the GSTT1 null genotype had a lower percent predicted FVC than those with the GSTT1 present genotype (98.8 ± 12.5% vs. 103.4 ± 11.4%, P = 0.012). To the best of our knowledge, this is the first report to suggest that the GSTT1 present genotype may be a risk factor for early airway injury in Japanese current smokers.

IDENTIFICATION OF TAMOXIFEN N'-GLUCURONIDE FROM BREAST CANCER PATIENTS TAKING TAMOXIFEN

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Tamoxifen (TAM), a nonsteroidal antiestrogen, is a widely used drug for chemotherapy of hormone-dependent breast cancer in women. Although initially effective, the problem with endocrine therapy with TAM is the inevitable development of antiestrogen resistance and mechanisms remain unknown. Recently, we have reported a new potential metabolic pathway of TAM and 4-hydroxy-TAM (4-HO-TAM), an active metabolite of TAM, via N-linked glucuronic acid conjugation in vitro. N-Glucuronidation of these substrates was catalyzed by UDP-glucuronosyltransferase 1A4 (UGT1A4). We have proposed that the new potential metabolic pathway of TAM might contribute to the biological activity of TAM in vivo. We have also found that overexpression of UGT1A4 in human MCF-7 breast cancer cells resulted in an acquired resistance to growth inhibition activity of TAM and 4-HO-TAM even the cells were still estrogen sensitive. In the present study, blood and urine samples from 10 breast cancer patients who had been taking TAM for at least 30 days were analyzed using HPLC/MS/MS to prove the existence of the metabolic pathway of TAM via N-glucuronidation in vivo. TAM N'-glucuronide was isolated by solid extraction from plasma and urine samples and identified with the synthetic specimen by HPLC/MS/MS. The present study provides the first evidence of TAM-N'-glucuronidation in human in vivo. Further quantitative analyses of the glucuronide in these samples are now in progress in our laboratory.