GSTM1 and GSTT1 polymorphisms in population-based study of colorectal cancer risk

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Introduction: Colorectal cancer (CRC) remains a significant cause of mortality accounting for 10% of all deaths of malignancies in European Caucasians. Glutathione S-transferases (GSTs) participate in the detoxification of chemotherapeutic agents used in therapy of CRC. Genetic polymorphisms in GST genes (copy-number variants of GSTM1 and GSTT1) that lead to diminished enzyme activity have been associated with CRC risk and survival increased chemotherapeutic treatment benefit in patients in most of the studies.
Aims: In this study we examined associations of GSTM1 and GSTT1 genotypes and clinical factors (age, gender, stage, localization of the tumor) with risk and we assessed the effect of genetic polymorphisms in GST genes on survival in CRC patients treated with adjuvant/palliative chemotherapy.
Materials & methods: We followed 1106 CRC patients treated with chemotherapy based on fluoropyrimidines and 1343 unrelated controls. Polymorphisms were genotyped by a relative quantification method (copy-number variants of GSTM1 and GSTT1), and PCR followed by gel electrophoresis (null/non-null genotypes for GSTM1 and GSTT1). Statistical evaluations of risk were evaluated using the Pearson Chi-Square Test. Associations between genotypes and overall survival were assessed using Kaplan-Meier curves and Cox proportional hazards regression.
Results: GSTT1 null was associated with a small but significant increase in risk ($p = 0.013$, OR = 1.393, 95% CI = 1.007-1.818). Copy-number variants of GSTM1 was associated with a reduction of risk (pDominant model < 0.001, OR = 0.673, 95% CI = 0.552-0.820). The same associations were founded in male cases after gender stratification.
There were no significant associations between GSTT1 and GSTM1 genotypes with other clinical factors (localization, stage and tumor node metastasis classification) in the total case group. However, following stratification by age (<70 vs ≥70 years at diagnosis), in young patients, GSTT1 null was associated with an increased risk ($p < 0.001$, OR = 1.942, 95% CI = 1.523-3.440).
Furthermore, GSTM1 null and GSTT1 copy number variation were associated with low survival rates in younger patients ($p = 0.047$, HR = 3.937; $p = 0.039$, HR = 4.246). However, survival increase is observed in young patients with GSTM1 copy number variant (pDominant model < 0.001, HR = 13.246).
Conclusions: This study confirms the association with the risk and the effect of GSTT1 and GSTM1 polymorphisms on survival in CRC patients who received chemotherapy.
We also suggest a specific risk association with GST null genotype in younger patients, particularly in those with presentation of tumor under the age of 70 years. The null GST genotype could be related to an improved immune response in younger patients, but less detoxification and increased rates of DNA damage in older patients.