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*GSTT*1 and *M*1 polymorphisms in Hürthle thyroid cancer patients

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Abstract

Glutathione S-transferases (GST) are an important part of cell defense against numerous genotoxic compounds and ROS. In order to test the possibility of association between the *GSTT1* and *M1* null allele variant, and the risk of TCO (thyroid carcinoma with cell oxyphilia), a case-control study was carried out. The rationale for our study was that according to the important roles of *GST* enzymes in cells and association of GST null genotypes with many types of tumors, inactivating polymorphisms may be genetic susceptibility factors in the etiology of oxyphilic thyroid tumors characterized by mitochondrial dysfunction, increased ROS production and resistance to chemio- and radio-therapy. We found the frequency of *GSTT1* null genotype of 19.2% in cases and 15.7% in controls, with an adjusted odds ratio (OR) of 1.4 (95% confidence interval (CI), 0.70–2.81), and a frequency of *GSTM1* null genotype of 59% in cases with oxyphilic tumors and of 55.6% in controls (OR 1.24; 95% CI, 0.62–2.48), indicating that the *GSTT1* and *M1* null genotypes do not increase the risk of development of oxyphilic tumors.

Keywords: Hürthle cell tumors; GSTT1; GSTM1; Polymorphism; Genetic susceptibility

1. Introduction

Thyroid tumors are the most frequently diagnosed malignancies among endocrine neoplasias. Risk factors for non-medullary thyroid carcinogenesis involve radiation exposure, hormonal factors (all thyroid diseases are 2–3 times more frequent in women than in men), iodine intake, previous thyroid pathology and hereditary factors [1–7]. However, all

Abbreviations: GSTT1, glutathione S-transferase T1; *GSTM1*, glutathione s-transferase M1; ROS, reactive oxygen species; OXPHOS, oxidative phosphorylation; MRC, mitochondrial respiratory chain; HCA, Hürthle cell adenomas; HCC, Hürthle cell carcinomas; PTC, papillary thyroid carcinoma; FvPTC, follicular variant of papillary thyroid carcinoma; mtDNA, mitochondrial DNA; NMTC, non-medullary thyroid carcinoma; OR, odds ratio.

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these factors cannot be considered separately, since they often cooperate in terms of interaction between environmental influence and individual genetic susceptibility to thyroid tumorigenesis [6,7].

Cell oxyphilia is a particular feature of many benign and also malignant conditions occurring in the thyroid, parathyroid, salivary glands and kidney. The presence of a large volume of granular eosinophilic cytoplasm, ultrastructurally characterized by mitochondrial hyperplasia with more than 75% of these cells in a tumor sample is the criterion for diagnosis of Hürthle cell neoplasms, the oxyphilic tumors of the thyroid. Oxyphilic features can be present both in papillary thyroid carcinoma (PTC) and in follicular tumors, namely Hürthle cell adenoma (HCA) or carcinoma (HCC). These tumors are very rare (less than 5% of all thyroid malignancies), but Hürthle cell carcinoma are clinically very aggressive and with considerably higher overall mortality rate than other non-medullary thyroid tumors [8]. Hürthle cell tumors are sporadic, but their occurrence in a familiar setting has also been reported [6]. The mechanisms that underlie mitochondrial hyperplasia and neoplastic development of this particular type of tumor are not well understood. However, it is well documented that key genes coding for proteins involved in energy production, proliferation and cell senescence from both nuclear and mitochondrial genomes of these cells are profoundly altered [9,10]. The defects in the apoptosis-inducing pathways can eventually lead to the expansion of population of neoplastic cells resistant to chemotherapy and irradiation, as in the case of HCC [11–13].

The mitochondrial respiratory chain (MRC) is a major source of reactive oxygen species (ROS) which are detrimental factors involved in the development of many human malignancies. Mitochondria are also direct targets of oxidative and chemical stresses that lead to mitochondrial and nuclear DNA mutations as well as to altered gene expression [14–18]. We have observed the increased production of ROS in oxyphilic carcinoma cell line, which may indicate that the necessary balance between pro- and anti-apoptotic triggering factors is deeply altered in HCC [19].

Cytoprotective mechanisms are complex and they include enzymatic and non-enzymatic mechanisms of cellular defense against oxidative stress [18,20]. The different glutathione S-transferase (GST) enzymes have classically been considered as an important part of the cell defense against numerous harmful chemicals and ROS produced endogenously and in the environment [21–25]. Their importance is suggested by the finding that mutations in *GST* genes have been associated with susceptibility to various diseases, in particular with cancer [21]. Both *GSTT1* and *GSTM1* null cells are more susceptible to sister chromatid exchange, following exposure to various electrophiles [20] The biological consequences of the failure to express functional GSTT1 and GSTM1 protein can also include susceptibility to cancer of lung, prostate and breast [25]. Presumably genotypes alone, or in combination, should identify individuals who are detoxification-deficient and consequently more likely to suffer the formation of carcinogen-DNA adducts and/or mutations [26].

The results obtained in three recently published studies [27–29] did not show a strong association between the GST polymorphisms and papillary and follicular thyroid cancer susceptibility. In these studies the authors showed that only the combination of *GSTM1* and *GSTT1* null inheritance [28] or only the presence of three potentially risk alleles, namely *GSTM1*-null, *GSTT1*-null and *GSTP1* Ile/Ile [29], leads to significant increase in adjusted odds ratio for papillary and follicular thyroid cancers. These results were not confirmed by the third study conducted on a Spanish population [27].

Individuals with *GST* null genotypes may have higher levels of glutathione (GSH) because of the reduced consumption of this tripeptide in GST-catalyzed reactions, or may as well have unrecognized effects on the expression of other enzymes involved in the maintenance of cellular GSH levels [30]. On the other hand, the increased production of ROS followed by alterations in energy metabolism and apoptosis emphasize the importance of glutathione-associated enzymes in oxyphilic carcinogenesis [31]. Both of these two aspects may be involved in chemo and radiotherapy resistance observed in HCC, as well as in incomplete execution of the apoptotic program in Hürthle cells, which has been the rationale for our study on this particular type of thyroid tumor.

According to the literature reviewed, so far no studies have been published on the association between *GST* polymorphisms and increased