GST gene polymorphisms and the risk of colorectal cancer development

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Increasingly often, molecular studies of colorectal cancer focus on low penetrance genes. Among the factors potentially modifying the risk of contracting colorectal cancer is the glutathione S-transferase (*GST*) gene family, encoding enzymes of the glutathione transferase type. Proteins of the GST family (glutathione S-transferases) are enzymes detoxifying a wide range of hazardous substances, such as reactive oxygen species (ROS) or xenobionts. Thus, their role, among other things, is the protection of DNA against oxidative damage, which may lead to mutations, and in consequence, favour carcinogenesis. *GST* gene polymorphisms may affect the functioning of the encoded enzymes, exerting an effect on the level of DNA damage, and therefore may have an indirect influence on the risk of the development of cancer. At present, there are many studies available concerning GST gene polymorphisms as factors modulating the risk of developing cancer, including colorectal cancer.

Key words: tumours, colorectal cancer, glutathione transferases, *GST* genes.

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Introduction

The scope of problems concerning colorectal cancer (CRC) in Poland and worldwide covers primarily two trends: molecular and epidemiological studies.

Among molecular studies there dominate investigations concerning the genetic conditioning of cancer, and the pathways of carcinogenesis. Also, the contribution of low penetrance genes in the modification of the risk of development of CRC is increasingly frequently examined. One such factor is the glutathione S-transferase (*GST*) gene family, encoding enzymes of the glutathione transferase type. *GST* gene polymorphism may exert an effect on the risk of development of CRC, especially in the context of diet and nutritional habits, by modification of the exposure of intestinal mucosa to food-related carcinogenic agents [1]. Red meat is a potential source of carcinogens, and the amount and duration of exposure to them may be modified by GST enzymes [1, 2]. Not long ago, a systematic review was published of studies concerning the analysis of the interactions between diet and genetic factors in the development of CRC, which did not provide an unequivocal conclusion, suggesting that further studies should be carried out in this area [1].

GST enzymes

Proteins of the GST family (glutathione S-transferases) are enzymes detoxifying a wide range of hazardous substances, such as reactive oxygen species (ROS) or xenobionts [3]. These enzymes catalyse the reaction of the conjugation of chemical compounds, of both exogenous and endogenous origin, with glutathione [4, 5]. Substances detoxified in this way include lipid peroxidation products, prostaglandins, various types of chemotherapeutics, and the majority of substances belonging to environmental carcinogens, such as heterocyclic aromatic amines [5]. The conjugation of electrophilic reagents with reduced glutathione, catalysed by GST enzymes, is aimed at limiting the possibilities of hazardous effects of these strongly reactive compounds on vitally important cell components, such as proteins or nucleic acids. The role of GST enzymes, among other things, is the protection of DNA against oxidative damage, which may lead to mutations, and in consequence, favour carcinogenesis [6].

These enzymes are classified into two superfamilies: cytoplasmic transferases, soluble, dimeric enzymes; and the so-called MAPEG superfamily (membrane-associated proteins in eicosanoid and glutathione metabolism), to which belong microsomal GST enzymes, membrane-bound, trimeric. Individual isoenzymes have no universal substrate, each of them belonging to both superfamilies, binding and neutralizing specific substrates; therefore, it is considered that all GST enzymes play an important role in the biotransformation of toxic compounds and chemical environmental agents [7].

From among 8 currently known classes of *GST* gene encoded enzymes, cytoplasmic transferases GSTM1 (μ), GSTT1 (θ) and GSTP1 (ϖ) are especially frequently examined, mainly due to the high frequency of polymorphisms within their genes, observed in various human populations [6, 7].

GST gene polymorphism

GST gene polymorphism may exert an effect on the functioning of enzymes encoded by these genes through the change in both the level of gene expression and activity of the protein itself. In this way it has an influence on the possibility of detoxification of carcinogens, and consequently, the level of DNA damage; thus it may have an indirect effect on the risk of development of cancer [6].

Polymorphism of *GSTM1* and *GSTT1* genes observed in the human population consists in hereditary homozygous deletion null/null – deletion of a gene fragment, resulting in lack of the protein product, which is related to the total loss of enzymatic activity. The *GSTM1* gene is located on chromosome 1p13.3 [8]. Deletion of a fragment of this chromosome of the length of 20 kb developed in the course of evolution as a result of recombination between two highly homologous fragments flanking the gene locus. In this way, there developed the deletion GSTM1 null genotype. Deficiency of GSTM1 transferase activity resulting from the above-mentioned genotype is observed in 30–50% of humans, according to population studies [6]. GSTM1 null genotype seems to be related to low capacity for the detoxification of selected xenobionts and reduced capability for controlling oxidative stress, which is equivalent to the damage to the cell caused by the activity of free radicals [8].

It is estimated that 10–20% of the Caucasian population are carriers of the GSTP1 null genotype [9].

GSTP1 gene polymorphism is most often a point mutation SNP (single nucleotide polymorphism) within exon 5 Ile_{105} Val. Thus, the results of mutation are GSTP1 genotypes Ile/Ile, Ile/Val and Val/Val [8]. The exchange of isoleucine and valine in the amino acid chain results in decreased enzymatic activity of protein [9].

Importance of *GST* gene polymorphism in the development of cancer

Many studies are available concerning the polymorphisms of *GST* genes as factors modulating the risk of contracting cancer, including gastrointestinal cancer. A meta-analysis of studies conducted in recent years on the Chinese population showed a relationship between GSTM1/GSTT1 null genotypes and an increased risk of development of hepatocellular carcinoma (HCC) [11].

In India, a study which covered more than 300 patients with gastrointestinal cancer confirmed that the GSTM1 null genotype is significantly related to an increased risk of rectal cancer and the GSTT1 null genotype to an increased risk of colon cancer. In addition, it was suggested that the concomitance of polymorphism in three genes, *GSTM1*, *GSTT1* and *GSTP1*, may be an important factor predisposing to the development of CRC in the Hindu population [12].

A further study conducted in Iran indicated the genotype GSTM1 null as predisposing to the development of CRC in individuals aged over 60 [13].

In the Lebanese population, a significantly increased risk of contracting gastric cancer and colorectal cancer was found in individuals with the GSTM1 null genotype. The researchers stated that these results corroborate the results of similar studies conducted on the Caucasian population [14].

Hlavata *et al.* suggested that the GSTM1 deletion is associated with a moderate increase in the risk of development of colorectal cancer in the Czech population, whereas the simultaneous deletion of the *GSTM1* and *GSTT1* genes causes a significantly higher risk of the development of CRC, compared to the presence of the complete sequence of both genes [15]. In turn, completely different results were obtained in another study, also conducted on a Czech population, where no statistically significant differences in the risk of development of CRC were found between various genotypes of GSTM1 and GSTT1 [9].

The lack of correlation between *GSTP1* gene polymorphism and the risk of development of CRC was confirmed in the studies by both Hlavata *et al.* [15], and Khabaz [10]. These researchers concur that *GSTP1* gene polymorphism does not exert any effect on the risk of contracting colorectal cancer. In the study by Khabaz, after analysing genotypes of 90 CRC tissue specimens and 56 specimens of healthy tissues of the large intestine, no statistically significant differences were observed between GSTP1 genotypes [10].

Also, Zhao *et al.* (China) in a meta-analysis of 30 various reports published in the Medline and Embase databases did not find any clear correlation between *GSTP1* gene polymorphism and the risk of colorectal adenoma (CRA). The researchers also suggested that (with some exceptions) *GSTT1* and *GSTM1* polymorphisms are not CRA risk factors [16].

It is noteworthy that many studies within this scope of problems concern the Asian population. It is known that ethnic differences are of great importance in the shaping of genetic predisposal for contracting cancer. The studies which confirm a correlation between GSTM1 null genotype and increased risk of prostate cancer in the Asian population are not reflected in the studies carried out on the Caucasian population. In the ethnic differences in the risk of developing the disease, both different conditions of the living environment of individuals belonging to a given population, and the genetic background are important [8]. The frequency of mutations within the *GST* genes in individual ethnic groups varies significantly. For example, the frequency of occurrence of *GSTT1* null genotype among the Caucasian population is approximately 0.20, whereas among the Asian population it is 0.52 [11]. These facts do not allow the projection of the results obtained in one ethnic group to the other.

Despite the researchers' great interest in this scope of problems, there is no consensus concerning the issue of importance of *GST* gene polymorphism for the development of colorectal cancer. The results of the analyses performed in various populations do not overlap, and

sometimes are even contradictory. This may possibly be due to the fact that the above-mentioned studies analyse the importance of individual genes of the GST family in the risk of developing colorectal cancer; however, they do not consider the effect of environmental factors, such as diet or tobacco smoking. Studies concerning the mutual correlation between these factors in the risk of development of CRC are still scarce.

Cotterchio *et al.* investigated SNPs in genes for 15 enzymes involved in the metabolism of carcinogens produced in heavily roasted meat, including GSTM1, GSTT1 and GSTP1. DNA for the study was isolated from peripheral blood lymphocytes. Differences were found in the importance of polymorphism of individual genes for the risk of development of CRC. Among other things, it was confirmed that GSTT1 gene polymorphism significantly modified the relationship between the consumption of red meat and CRC risk, while *GSTM1* gene polymorphism did not change this risk [17]. In turn, in a systematic review of over 2,500 studies analysing the interactions between diet and genetic factors in the risk of development of CRC, a relationship is suggested between both *GSTT1* and *GSTM1* gene polymorphism and dietary factors; however, this thesis requires confirmation by further, independent prospective studies [1].

To sum up, the large number of studies concerning *GST* gene polymorphisms in colorectal cancer indicates that in recent years the researchers' interest within this scope of problems has been great. The results of studies conducted worldwide vary, which may be associated with both genetic differences between human races, and very difficult to grasp factors related to life style and exposure to various environmental factors. Nevertheless, a relationship is suggested between *GST* gene polymorphism and the development of cancers of the gastrointestinal tract. Therefore, further studies on this gene family are justifiable, and in the future may help to develop effective prophylactic programmes for colorectal cancer.

Authors declare no conflict of interest.

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