Rezumat

Variante genice ale GSTM1, GSTT1 și GSTP1 în cancerele urologice multiple

Introducere: Glutation S-transferazele (GST s) sunt enzime de faza a II-a, răspunzătoare de catalizarea biotransformării unei mari varietăți de compuși electrofili având un rol central în detoxificarea metaboliților activi ai procarcinogenilor produs din reacțiile de faza I, prin legarea lor de glutation și favorizarea excreției acestora prin urină.

Obiective: am evaluat genotipurile GSTM1, GSTT1 și GSTP1 la pacienții pacienții diagnosticați cu tumori maligne multiple, dintre care cel puțin una a fost localizată la nivelul prostatei, vezicii urinare sau rinichiului.

Material și metodă: am evaluat genetic pentru genotipurile GSTM1, GSTT1 și GSTP1 34 pacienți cu cancere multiple urologice și 23 pacienți cu asocierea unui cancer urologic cu un alt tip de cancer. Rezultate: în lotul pacienților cu cancere urologice multiple genotipul nul GSTT1 a fost constatat la 26,4% dintre pacienți, comparativ cu 0% la martori; cel puțin un genotip nul GSTM1 sau GSTT1 a avut 82,35% dintre pacienți comparativ cu 47% martori; în lotul cu cancere diferite genotipul nul GSTM1 a fost constatat la 52,1% dintre pacienți, comparativ cu 4,3% la martori; genotipul nul GSTT1 a fost găsit la 34,7% dintre pacienți, comparativ cu 4,3% dintre martori; cel puțin un genotip nul GSTm1 sau GSTT1 a fost constatat la 73,9%, comparativ cu 8,6% în rândul martorilor.

Concluzii: Genotipul nul GSTT1 este un factor de risc pentru pacienții având mai multe tumori maligne primitive urologice (de vezică urină, prostată și rinichiu); genotipul nul GSTM1 sau GSTT1 este mai frecvent întâlnit la pacienții cu neoplazii multiple urologice; genotipul nul GSTM1 și GSTT1 reprezintă factori de risc pentru pacienții cu tipuri diferite de cancer, cel puțin unul fiind în sfera urinară.

Cuvinte cheie: cancere multiple, cancere urologice, GSTM1, GSTT1, GSTP1

GSTM1, GSTT1 and GSTP1 Genetic Variants in Multiple Urologic Cancers

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Abstract

Introduction: Glutathione S-transferases (GSTs) are phase 2 enzymes responsible for catalyzing the biotransformation of a wide variety of electrophilic compounds, having a crucial role in the detoxification of active metabolites of procarcinogens produced by phase 1 reactions, tying them to glutathione and promoting their excretion in the urine.

Objectives: we evaluated GSTM1, GSTT1 and GSTP1 genotypes in patients diagnosed with multiple malignancies, of which at least one was found in the prostate, bladder or kidney.
Materials and methods: GSTM1, GSTT1 and GSTP1 genotypes were genetically assessed in 34 patients with multiple urologic cancers and 23 patients with urologic cancer associated with another type of cancer.

Results: in the group of patients with multiple urologic cancers, GSTT1 null genotype was found in 26.4% of patients compared to 0% in controls, 82.35% of patients and 47% of witnesses carried at least one GSTM1 or GSTT1 null genotype, and in the group with different cancers, GSTM1 null genotype was found in 52.1% of patients compared to 4.3% of witnesses in the control group; GSTT1 null genotype was found in 34.7% of patients compared to 4.3% of witnesses, at least one GSTM1 or GSTT1 null genotype was found in 73.9% of patients compared to 8.6% of controls.

Conclusions: GSTT1 null genotype is a risk factor for patients with more primitive urologic malignancies (bladder, prostate and kidney); GSTM1 or GSTT1 null genotype is more frequent in patients with multiple urologic tumors; GSTM1 and GSTT1 null genotypes are risk factors in patients with different types of cancer, with at least one affecting the urinary system.

Key words: multiple cancers, urologic cancers, GSTM1, GSTT1, GSTP1

Introduction
The incidence of cancers in the urinary system has increased in recent years, particularly prostate cancer, which is the second most frequently diagnosed cancer in the world. Careful medical and urologic supervision, as well as modern means of investigation for these malignancies, allow for the diagnosis of a second cancer, often found in the urinary system as well, probably developing due to the existence of common risk factors, including genetic predisposition, or to the multifocal nature of transitional cell carcinomas, which are predominant in kidney and bladder cancers.

Working hypothesis. Objectives
The increased number of patients with multiple primitive urologic tumors diagnosed either simultaneously or at a variable interval of time, synchronous and metachronous, triggered the question of whether they have a connection with possible genetic changes in the three GSTs, known in the literature as being associated with various forms of cancers, including bladder, prostate and kidney cancers. We examined these patients with multiple cancers in comparison with a witness group to see if there are significant differences in GSTM1, GSTT1 and GSTP1 genetic variants.

Materials and methods
The study regarded patients diagnosed between 2005 and 2012 in Cluj-Napoca County Clinic Hospital with several distinct primitive cancers, of which at least one was found in the bladder, prostate or kidney. We studied GSTM1, GSTT1 and GSTP1 genetic variants in patients identified with multiple urologic malignancies and in those who have been diagnosed with a urologic cancer associated with another type of cancer. The total number of patients with urologic pathology (1), among which were chosen mostly those with multiple primitive cancers, was: 923 (18.44%) patients with prostate cancer, 868 (17.34%) patients with bladder cancer, 454 (9.07%) patients with renal cancer, 112 (2.23%) patients with testicular cancer, 195 (3.89%) patients with history of cancer found in the urinary system. Thirty-six patients (16.58%) had at least two distinct urologic malignancies and other 34 patients (15.66%) had a combination of urologic cancer and another cancer with a different location. The genetic study was conducted on 34 patients of the 36 identified with at least two distinct urologic malignant tumors, as two of them expressed their rejection. Of the 34 patients with various cancers, of which only one was found in the urinary system, 23 were analyzed, 5 patients had broken genetic material (obtained by DNA extraction from paraffin embedded biopsy samples) and some of them refused peripheral blood sampling (6 patients). The results of the genetic analysis of the two groups thus formed were compared with those obtained by genetic material processing in two corresponding groups of healthy controls, similar in age.

Patient clinical data were obtained from clinical observation sheets. Inclusion criteria in the study were: cases with at least two histologically verified primitive malignant tumors, of which at least one was found in the urinary system, regardless of the time of diagnosis (simultaneous, synchronous or metachronous); when there was clear histopathologic evidence of index tumor (in some cases being diagnosed many years before) we took into account the existence of adjuvant therapies, such as radiotherapy and chemotherapy, as factor supporting the diagnosis of malignancy. Exclusion criteria were the following: cases where more distinct malignant tumors of the bladder were diagnosed, sometimes dozens, knowing their multicentricity; cases where metastasis could not be excluded, even when three apparently distinct malignant tumors were present, found in three urinary organs, but having the same histopathology.

Patients included in the study signed their informed consent. There have also been cases (for patients who died) when the patient’s preoperatively signed consent was used, which implied acceptance on the use of data and materials collected as anonymous. The genetic material was obtained by sampling 2 ml of peripheral blood or by paraffin-embedded biopsy samples. Genetic analysis consisted of genotyping GSTM1, GSTT1 and GSTP1, comparing the groups included

8 The figures in parentheses represent the percentage of patients diagnosed with at least two primitive malignant tumors found in the urinary system, out of the 217 cases of patients diagnosed with multiple primitive cancers throughout the 7 ½-year period.
in the study with an adequate number of healthy controls with similar age, using chi-square test for statistical analysis.

We extracted the DNA of all the patients and controls from a quantity of 2 ml peripheral blood (on EDTA) or from paraffin embedded sample. This study was approved by Clinic County Hospital Ethic Board. For the DNA extraction from paraffin embedded samples we used a QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany) based on protocol provided by the manufacturer. We used xylene in order to remove the paraffin, then ethanol for rehydrating the samples, then the incubation with proteinase K, purified on QIAamp MinElute column and eluted in nuclease free water; we measured the DNA concentrations with a Nanodrop spectrophotometer (NanoDrop Technologies; Wilmington, DE).

Some patients had a fragmented DNA which made impossible the search for genetic polymorphisms.

The absolute absence of the specific enzymes implicated in metabolic detoxification of carcinogens results in null GSTM1 and GSTT1 genotypes, and for the GSTP1 Ile105Val polymorphism. The genetic polymorphisms of GSTM1 and GSTT1 were determined simultaneously using a multiplex PCR protocol (2). We could not make the difference between heterozygous (+/0) and homozygous (+/+ ) genotype (both allele or only one allele without mutation), being able to determine null genotypes (-/-). We used three different primers for the amplification of both GSTM1 and GSTT1 allele (FwM1 5'-GAACTC CCTGAAAAGCT AAAGC-3'; RevM1 5'- GTTGGGCTCAAA T A T AGGGTGG - 3'and FwT1 5'- TTCTTTACT GGTTCCTCACATCTC-3'; RevT1 5'- TCAC CGGATCATGOC CAGCA-3'), also using an internal control, the amplification of β Globin. The gradient thermocycler (MastercyclerGradient, Eppendorf®, Germany) was used for PCR reactions. We obtained a total amount of approximately 100 ng of genomic DNA, amplified then in a total volume of 25 μl reaction mixture containing 12.5 μl 2xPCR Master Mix (Fermentas MBI, Lituania®), 1 μl BSA (Bovine Serum Albumine, Fermentas MBI, Lituania®) solution 5 mg/ml, 8 pM of each primer, forward and reverse (Eurogentec, Belgium®) and water free of nucleases to complete the 25 μl reaction volume. For analysing the amplification products we used electrophoresis in MetaPhor agarose gel (Lonza®, Basel, Switzerland).

The amplified fragment of 176 bp, result of the PCR reaction, was digested with 5 U BsmAI (Fermentas MBI, Lituania®); then we separated the fragments on a 3.0% Metaphor® agarose gel (Lonza®, Basel, Switzerland), and visualized them in a UV transilluminator (VilberLourmat Imaging System®, Marne-la-Vallee, France) after staining with ethidium bromide. We obtained three fragments of 176, 91 and 85 bp (the Ile/Val genotype), two fragments of 91 and 85 bp (a Val/Val homozygous genotype), or an undigested product (4) of 176 bp (an Ile/Ile genotype).

Results

Among the 34 patients, 14 presented an association of bladder cancer with prostate cancer, 10 had both bladder cancer and kidney cancer, 8 had both prostate cancer and kidney cancer, and 2 had bilateral renal cancer. The most common urologic index tumor was prostate cancer, followed by kidney and bladder cancer, respectively. In 11 cases, the tumors were synchronous. The second distinct primitive malignant tumor appeared after an average period of about 5 years. Of the 23 patients with malignant tumors in the urinary system, associated with other primitive cancers, 11 had kidney cancer, 8 bladder cancer and 4 had prostate cancer. The other primitive malignant tumors were: 8 colorectal cancers, 5 lymphomas, 4 breast cancers, 3 malignant melanomas, one gastric cancer, one laryngeal cancer, and one non melanoma skin cancer.

We examined 34 patients with two neoplasms in the urinary system in comparison with 34 controls with similar age (±2 years) to that of cancer patients. The average age at the occurrence of the second neoplasm in the urinary system was 68.8 ± 9.02 years (ranging between 48 and 87 years). The average age in the witness group was 67.46 ± 11.39 years (ranging between 48 and 85 years). The average age at first cancer diagnosis was 64.5 ± 9.9 years (ranging between 41 and 84 years). The ages of patients and witnesses had a normal distribution (Kolomono-Smirnov test). There were no statistically significant differences between the average age of patients at study enrollment and that of controls (t test for independent variables, p=0.5). The location of the first cancer was in the prostate for 11 patients (32.3%), kidney for 12 patients (35.2%) and in the bladder for 11 patients (32.3%). The location of the second cancer was in the prostate for 10 patients (29.4%), kidney for 9 patients (26.4%) and in the bladder for 15 patients (44.1%). There were 19 smokers in the case group (55.8%) and 16 smokers in the control group (47.9%), without any statistically significant difference (chi-square test, p=0.6). GSTM1 null allele was found in 23 patients (67.6%) and in 16 controls (47%), without any statistically significant differences between the two groups (chi-square test, p=0.1). In the group with cancers, the genetic analysis revealed the presence of Ile/Ile common homozygous variant of GSTP1 polymorphism at position 105 in 13 patients (38.2%), Ile/Val heterozygous variant in 15 patients (44.1%) and Val/Val homozygous variant in 2 patients (5.8%). In the control group, we found the Ile/Ile homozygous
variant of GSTP1 at position 105 in 19 subjects (55.8%), Ile/Val heterozygous variant in 15 subjects (44.1%) and Val/Val homozygous variant in none of the subjects. Alleles were in Hardy-Weinberg equilibrium (chi-square test = 0, p=0.9). There were no statistically significant differences in allele frequency between the case group and the controls (chi-square test, p=0.4). For GSTM1, there were no statistically significant differences in null allele frequencies between different cancer locations in the urinary system (chi-square test, p>0.05). For GSTT1, there were no statistically significant differences in null allele frequency between the various cancer locations in the urinary system (chi-square test, p>0.05). GSTP1 genotype frequency (common and variant in position 105) did not differ between various cancer locations in the urinary system (chi-square test, p>0.05). GSTT1 null genotype was found in 9 patients (26.4%) but in no witness, with statistically significant differences between the groups (chi-square test, p=0.002). At least one null genotype (GSTM1 or GSTT1) was found in 28 patients (82.35%) in the case group, and in 16 subjects (47%) in the witness group, revealing a statistically significant difference (chi-square test, p=0.005). In the case group, 4 patients (11.7%) carried a null genotype for both GSTM1 and GSTT1, but the differences were not statistically significant (chi-square test, p=0.1).

Another group consisted of 23 patients with a cancer in the urinary system associated with a second cancer of a different location than the urinary system, together with 23 controls close in age (±2 years) to cancer patients. The average baseline age of patients with multiple malignancies was 65.22 ± 8.2 years (ranging between 50 and 78 years). The average age for the witness group was 64.61 ± 10.8 years (ranging between 50 and 82 years). The average age at the onset of the first cancer was 58.52 ± 10.1 years (ranging between 41 and 78 years). Patient and witness age had a normal distribution (Kolomorov-Smirnov test). There were no statistically significant differences between the average age of the patients at study enrollment and that of the controls (t test for independent variables, t=0.8). The study included 14 women (30%) and 32 men (69.5%). There were 12 smokers among the patients (52.1%) and 13 smokers among the controls (56.2%). The percentage of smokers was not statistically significantly higher in the case group compared to the control group (chi-square test, p=1). GSTM1 null genotype was found in 12 patients (52.1%) and in 1 control (4.3%), revealing statistically significant differences (chi-square test, p=0.001). GSTT1 null genotype was found in 8 patients (34.7%) and in 1 control (4.3%), revealing statistically significant differences (chi-square test, p=0.02). The cancer group noted the presence of the common homozygous variant Ile/Ile of the GSTP1 polymorphism at position 105 in 9 patients (50 %), of the heterozygous variant Ile/Val in 7 patients (38.8%) and of the homozygous variant Val/Val in 2 patients (11%). In the control group, the homozygous variant Ile/Ile of the GSTP1 polymorphism at position 105 was found in 11 subjects (47.8%), the heterozygous variant Ile/Val in 12 subjects (52.2%) and the Val/Val genotype was not found in any of the subjects. Alleles were in Hardy-Weinberg equilibrium (chi-square test = 0.9, p=0.4). There were no statistically significant differences in genotype frequency between the patient group and the controls (chi-square test, p=0.2). Seventeen patients (73.9%) in the case group and 2 subjects (8.6%) in the control group carried at least one null genotype (GSTM1 and GSTT1), the percentage difference being statistically significant (chi-square test, p=0.005). In the case group, 3 patients (13%) carried both null genotypes (GSTM1 and GSTT1). The percentage difference was not statistically significant (chi-square test, p=0.2).

Discussion

Globally, prostate cancer is currently second in men (899,000 new cases, representing 13.6% of the total) and fifth overall. In 2008, it was the sixth cancer leading cause of death in men (6.1% of the total). In 2008, Romania (5) had an incidence rate of 19.9 per 100,000 inhabitants (3,620 cases) and a mortality rate of 8.9 (1,757 deaths). U.S. estimates for 2012 rank prostate cancer first (29% of all cancers), bladder cancer fourth (7% of all cancers) and kidney cancer sixth (5% of all cancers) in men, and in women kidney cancer alone represents 3% of all cancers diagnosed, being ranked eighth (6). Mortality rates for cancers of the urinary system rank prostate cancer second (9%) after lung cancer, bladder cancer eighth (3% of all cancers) and kidney cancer tenth (3% of all cancer deaths) in men. Bladder cancer has the following risk factors: smoking (accounting for 50-65% of cases occurring in men and 20-30% of those occurring in women), occupational exposure to aromatic amines, and to a lesser extent cyclophosphamide-based chemotherapy, analgesics containing phenacetin, ionizing radiation, and high levels of arsenic in drinking water (7). Risk factors for kidney cancer include smoking, obesity and hypertension (8-10) (considering that around 20-40% of kidney cancers in men and 10-20% of those in women are due to smoking, 20% to overweight), dialysis (11) (3-26 times increased risk compared to the general population), some syndromes (von Hippel-Lindau). The most common are individuals with two tumors among patients with multiple primitive cancers, those with three distinct tumors only being diagnosed in about 0.5% of patients, and patients with four or five primitive malignancies account for less than 0.1% of the population (12-15). Among our patients, with at least one cancer of the urinary system, five (0.2%) developed three distinct primitive malignancies (16).

From the patients with bladder cancer in our study, 5.18% have developed a second malignant primitive tumor. From those with prostate cancer, 4.11% have also developed other malignant tumors. From the patients with kidney cancer, 10.57% have developed other cancers, either before or after kidney cancer. Some studies have demonstrated an association of up to 70% of prostate cancer in patients with bladder cancer and of 3.4 % of bladder cancers in patients with prostate cancer (17). The literature reveals a low overall risk of developing other primitive malignancies, secondary to prostate cancer (18-21). In our study, 8 patients developed bladder cancer after one prostate cancer, after an average time interval
of three years. It is considered that radiotherapy is one of the factors that may contribute to the development of bladder cancer (22, 23), or other cancers (24-27), after prostate cancer. The number of cases in our study is too small to make relevant assumptions on the role of radiotherapy in further cancer development, but it is likely that such a study conducted at national level might offer a clearer picture. The average latency period between exposure to radiation and the development of bladder cancer is 30 years for low doses and 16.5 years for higher doses (28), although recently it has been reported to be shortened to 5 years (29). In our cases, we could not establish a causal relationship between the therapy applied for prostate cancer and the occurrence of bladder cancer, especially since the average time elapsed between the occurrence of the two primitive malignancies was low (3 years). The patients in our study revealed a higher frequency of either synchronous (in 4 patients renal cell cancer was synchronous with bladder or prostate cancer, in 3 patients bladder cancer was synchronous with prostate cancer) or metachronous association between prostate and bladder cancer, as well as between kidney and bladder or prostate cancers. Urologic cancer associations with other primitive malignant tumors were fewer (most commonly involving the colon, then the breast, hematologic cancers such as lymphomas or leukemia, melanoma and non melanoma skin cancers, larynx). The result of the assessment of all patients with urologic cancers shows that the most common cancer in this area has been bladder cancer, followed by prostate and then by kidney cancers, the most frequently cited in the literature being prostate cancers (30).

GSTs are phase 2 enzymes responsible for catalyzing the biotransformation of a wide variety of electrophilic compounds, thus playing a central role in the detoxification of active metabolites of procarcinogens produced by phase 1 reactions (31). So far, the studies conducted have shown an increase in the GSTM1 null genotype from 47% to 58%, as well as in the GSTT1 null genotype from 13% to 25% in the white European population (32-34), and even up to 80% in Asians. The heterozygous genotype Ile105Val of GSTP1 showed an increase from 38% to 45.7% and the homozygous genotype Val105Val from 7% to 13% (35). The frequency of GSTP1 genotype at position 105 in the Caucasian population was found to be 51.5% Ile/Ile, 39.4% Ile/Val and 9.1% Val/Val (36). It is said that GSTM1 in particular, as well as GSTT1, may be involved in the etiology of cancer in general, and not just one in particular (37). In our study, we found it is a risk factor for multiple colorectal cancers (38). Some studies have shown an increased risk for prostate cancer (39-44) associated with polymorphisms in GST genes, although some recent meta-analysis have reported that GSTM1, GSTT1 and GSTP1 polymorphisms are not major determinants of an increased susceptibility to prostate cancer (45). But the risk can become significant in combination with other factors (smoking). Recent studies have observed an increased risk for bladder cancer in GSTM1 null genotype (46-48), the risk being double in association with GSTT1 null genotype, especially in smokers (49). Even if GSTM1 null genotype causes an increased risk of solid tumors (50-53), we have not found an increased risk in patients with urologic cancers. We found GSTT1 null genotype in association with an increased susceptibility to urologic cancers, like other authors (54-58). The variant genotype of GSTP1 is associated with a risk for developing bladder cancer (59, 60). Our patients with multiple urologic cancers revealed no statistically significant differences for GSTP1 polymorphism, but they had a rate of about 50% of at least one modified allele at position 105.

The 23 patients in our second group had other types of cancer, most often colorectal cancer, as well as others (lymphoma, melanoma, breast, gastric, laryngeal, skin cancer), these types of cancers being associated with GSTM1 and GSTT1 polymorphisms (61-64). Although our patients with multiple urologic cancers, compared with controls, had a higher proportion of the GSTM1 null genotype (67.6% versus 47%), this difference was not statistically significant (p=0.1), we found that GSTT1 for these patients was significantly more frequent as null genotype (26.4%, p=0.002).

Statistically significant results have also been obtained in patients who had at least one GSTM1 or GSTT1 null genotype (82.35% vs. 47% for controls, p=0.005). Therefore, we can say that for patients with multiple urinary tumors, GSTT1 and partly GSTM1 may be risk factors. In patients with urologic cancers (kidney, prostate, bladder) associated with other cancers, both GSTM1 null genotype (52.1% versus 4.3%, p=0.001) and GSTT1 null genotype (47.7% versus 4.3%, p=0.002) were more frequent. The presence of any of the GSTM1 or GSTT1 null genotypes represented a risk factor (73.9% vs. 8.6%, p=0.005) in patients with multiple urologic cancers. GSTM1 null genotype may have contributed especially to the development of the other cancers, not so much to that of urologic cancers. We could not assess the contribution of each type of cancer found in the urinary system depending on the association with altered GSTM1, GSTT1 and GSTP1 genotypes. GSTM1 null genotype was found in 18 patients who had at least one bladder cancer, in 20 patients who had at least one prostate cancer, and in 20 patients who suffered from at least one kidney cancer. GSTT1 null genotype was present in 8 patients who developed at least one bladder cancer, in 8 patients who had prostate cancer, and in 10 patients with one primitive malignant tumor in the kidney. Heterozygous GSTP1 Ile105Val genotype was found in 13 patients with bladder cancer, in 9 patients with prostate cancer, and in 13 patients with kidney cancer. Homozygous GSTP1 Val105Val genotype was found in one patient with bladder cancer, in one with prostate adenocarcinoma, and in two patients with one of the cancers found in the kidney.

Conclusions

GSTT1 null genotype is a risk factor for patients with multiple malignant primitive urologic tumors (bladder, prostate and kidney). GSTM1 and GSTT1 null genotypes are more frequent in patients with multiple urologic malignancies. GSTM1 and GSTT1 null genotypes are risk factors in patients with different types of cancer, of which at least
one is in the urinary system. It is possible that the results linked to the GSTM1 null genotype may be due to other cancers, not to the one found in the urinary system (in the bladder, kidney or prostate). GSTM1 null genotype and GSTP1 variant genotype were not risk factors in patients with multiple urologic cancers.

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Conflict of interest

We declare that there is no conflict of interest for this manuscript. The work described is original and has not been published previously, and not under consideration for publication elsewhere.

References


