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Polymorphism of the glutathione S-transferases in prostate cancer

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Abstract:

Prostate cancer occurs more and more frequently in men over 50 years of age. Its etiology is still unclear, despite numerous studies of its main risk factors. Scientists discovered, that it is genetically and environmentally determined.

Recent publications suggest the role of S-glutathione transferases (GSTs) in modulation of prostate cancer risk. Numerous studies try to reveal the role of three the best known genetic variants, GSTM1, GSTT1 and GSTP1. Glutathione S-transferases as a multi-family of metabolic enzymes of the II-phase, are responsible for detoxification of various, potentially carcinogenic compounds. Deficiencies or changed activity of the enzymes, may increase the risk of mutation. The GSTs could be important in the etiology of cancers, including prostate cancer.

Numerous study suggest the influence of GSTM1, GSTT1 and GSTP1 polimorphisms on susceptibility to prostate cancer, while others, exclude such correlation. Therefore determining the significance of these genetic variants in prostate cancer should be the subject of further extensive research.

Keywords : Glutathione Transferase; Prostatic Neoplasms; Metabolic Detoxication, Phase II

1. Etiology of the prostate cancer.

Prostate cancer is a common disease, which mainly affects men over 50 years. According to the publications, it is the second cause of death (11%) in men because of cancer, the first is lung cancer [1, 2]. Annually, in Poland the 7200 cases is diagnosed and the number of diagnoses increases with age of patients. Peak incidence is between 65 and 79 years of age and despite good progress in treating patients, the prostate cancer could impair the quality of their life and results in numerous complications [2].
The etiology of this disease was not determined so far, despite studies of well-established risk factors such as age, ethnicity and geographical origin and family history of prostate cancer [3]. According to the studies, a patient, which father or brother suffered from prostate cancer, has doubly increased risk of developing the disease, than the general population. In turn, black men have the greatest risk of prostate cancer among different ethnic groups. While Hispanics are less likely to develop the disease, than Caucasian men [2].
Other risk factors include environmental impact, both factors on which man was exposed in place of residence or at work [2]. Last studies pay attention to the impact of such exposition as smoking, unhealthy diet or the exposure to carcinogens. It is believed, that environmental hazards can have a significant impact on carcinogenesis, including prostate. Moreover, individual differences resulting from the genetic profile

of efficient carcinogens detoxification have also been studied, what may help to understand different response of the human bodies on the impact of xenobiotics [3].
Studies of prostate cancer focus on the possible existence of genetic susceptibility to environmental hazards. Scientists searching for various polymorphisms, which play a role in metabolic activation or detoxification of exogenous carcinogens. Most publications focus on biotransformation enzymes such as GSTs or genes of cytochrome P450 [4].
Prostate cancer as a multifactorial disease include complex interaction of the environmental influence and the genetics, while the identification of the impact of selected carcinogens or genes responsible for impaired detoxification and the pathways of carcinogenesis are still important part of the future studies, which could result in the definition of prostate cancer etiology.

2. The role of the glutathione S-transferases

The glutathione S-transferases are a multi-gene family, which is responsible for the production of II-phase enzymes of xenobiotic metabolism [1, 4.]. These proteins catalyze a conjugation of glutathione with electrophilic compounds, mediating in the removal of endo- and exogenous substances from the body, also a carcinogens [5].
The example of carcinogenic substance, where GSTs enzymes play a role in its inactivation, are polycyclic aromatic hydrocarbons (PAH), which are a component of cigarette smoke, grilled meat or diesel. The GSTs also participate in detoxification of the reactive oxygen species and endogenous metabolites of steroid hormones [6]. Among a function of the GSTs is a role in a modulation of other enzymes induction, for example important in the processes of DNA repairing [1].
The GSTs enzymes are encoded by at least 8 separate loci and each of them has one or more homodimeric or heterodimeric isoforms. The most widely described are three loci: GSTT1, GSTM1 i GSTP1 [1]. Among these loci there are two deletion variants of GSTs (GSTT1 and GSTM1), which results in the lack of enzymatic activity and one polymorphism resulting from substitution within the active site of the enzyme (GSTP1), what leads to changes in conjugation activity and in substrate-specific thermal stability [5].
The GSTs enzymes are primarily involved in xenobiotics metabolism, including different types of potential carcinogens. Therefore, they have assigned role in body defense against toxic and carcinogenic substances, which are introduced into the body as a pollution, drugs or food additives. It is suggested that persons possessing the lack of function genes or genes of changed enzymatic activity might have limited ability to efficient elimination of carcinogens, what can leads to the accumulation of such components and increased risk of mutation as the consequences [4].

2.1. The GSTM1

The GSTM1 gene encodes information about glutathione S-transferase, which belongs to the "mu" class. Among its function is the detoxification of electrophilic compounds, such as drugs, different types of carcinogens (benzo[a]pyrene- smoke component) , environmental toxins and the products of the oxidative stress. This is done by conjugation with the glutathione, in the II-phase of xenobiotic's metabolism [4, 7].

The genes encoding the "mu" class are placed in gene's cluster on the chromosome 1q13,3 and are characterized by high polymorphicity. It is believed, that those genes can moderate susceptibility to carcinogens and toxins and the reaction of an organism to some drugs. Because of alleged heightened sensitivity of the organism on carcinogenic effect of the environmental toxins, they are suspected of connection with increased risk for some cancers [7].
It has been demonstrated, that the inheritance of GSTM1 deletion, the homozygous "null" variant of this gene, lead to the lack of this form of enzyme's activity. It is believed, that the "null" genotype, having a decreased ability to detoxification of selected carcinogens, might be connected to increased risk for solid tumors [3, 4].
Studies established the frequency of this gene in Caucasians in the range of 13,1- 54,5% [1]. In turn, the study of Slovac scientists cites a data about the frequency of GSTM1 polymorphism in the range of 47% to 58% in among white Europeans [3].

2.2. The GSTT1

The GSTT1 gene- theta 1, placed on the chromosome 22q11.23, is a member of protein's superfamily, which catalyzes the conjugation of reduced glutathione with various hydrophobic and electrophilic chemicals. Its possible role in carcinogenic process is emphasized. A function of the GSTT1 is detoxification of small, reactive hydrocarbons such as the ethylene oxide [4, 8].
The "null" genotype of GSTT1, as in the case of GSTM1 "null" polymorphism, leads to the lack of enzymatic activity of a protein. It is believed, that because of decreased ability to detoxification of ethylene oxide's metabolites , this genetic variant may provide an information about exposition to environmental or nutritional factors, which can cause a damages of a genetic material [4].
Deletion of the GSTT1 gene was combined with increased risk of ovarian, bladder or lung cancer. The frequency of homozygous deletion of this gene was estimated at 11-28,6% in Caucasians, while Slovac's study shows the frequency in the range of 13 to 25% in white Europeans [3].

2.3. The GSTP1

The GSTP1 is considered to be one of the main enzyme, involved in inactivation of substances in cigarettes and cigarette smoke, which have a carcinogenic effect. Among substances, which are neutralized by the GSTP1 are epoxide-benzo[a]pyrene diol and acrolein, a compound which is common environmental pollution and has a high reactivity with the cells of the organism [9, 10]. Additionally, researchers noticed, that this gene is inactivated by hypermethylation in the early stages of prostate carcinogenesis, and its expression is also disturbed in the samples of other cancers, what can suggest its role in cancers etiology [9].
Ile105Val, the most widely studied GSTP1 polymorphism, results from the substitution of isoleucine in valine at codone 205, and its consequence is probably the change in thermal stability specific for substrate and disturbed conjugation activity. The GSTP1 105Val variant was associated with decreased detoxification of some diols epoxide of polycycic aromatic hydrocarbons, when it was compared to GSTP1 105Ile variant [5].
According to the meta-analysis of Mo et al. 2009, the frequency of this polymorphism, which is placed on 11q13 chromosome, is estimated at 38,9-62,1% for homozygous

variant Val/Val in Caucasians. In turn, Sironova et al. [2009] shows the data for white Europeans about the frequency in the range of 38%, to 45,7% for Ile/Val heterozygotes and 7% to 13% for Val/Val homozygotes [1, 3].

3. The result of available researches and meta-analyses

A role of some antioxidant enzymes is widely studied in etiology of prostate cancer, because of its function in detoxification of potential carcinogens and the reactive oxygen species (ROS). The glutathione S-transferases are interesting research goals, because of its wide substrate specificity. At present the GSTs polymorphisms (GSTM1, GSTT1 and GSTP1) are widely studied, because they result in reduction or the lack of enzymatic activity GSTM1. Reports of those genetic variant's association with cancers suggest their role in etiology of colon, breast, lung cancer or prostate cancer as well [5]. The available publications showed high levels of the GSTs, as more efficient form of detoxification some chemical carcinogens, which protects a tissue against the DNA damages. Therefore it is suspected, that persons with GSTT1 or GSTM1 deletion variants or changed form of GSTP, could have limited ability to efficient elimination of some carcinogens, what could results in formation changes in the DNA [4]. It is interesting, that according to reports, persons with prostate cancer have lower levels of the GST enzyme in prostate tissue, when compared to the control group. It is also believed, that the tumor tissues can contain larger amounts of the ROS and oxidative lesions of the DNA strands. Many researchers believes, that the GSTs (GSTM1, GSTT1,GSTP1) polymorphisms are responsible for this effect, because they can be the reason of limited function of the oxidative lesions repairing [5].
Last meta-analysis of Mo et al. 2009 shows positive correlation for deletion variant GSTM1, unlike previous meta-analysis (Ntais et. al. 2005), which excluded the association of GSTM1, GSTT1 and GSTP1 with prostate cancer. In collective publication by Mo et al., based on an analysis of many studies, reported that the GSTM1 polymorphism increased the risk of prostate cancer based on large population, when compared to general population. Such associations have not been shown for GSTT1 or GSTP1 variants, based on the data collected for the populations of Asians, Caucasians, African Americans and Africans, respectively [1, 12].
The same results were from further study of this subject, which reported that the association of increased risk of prostate cancer in Koreans with null GSTM1 phenotype is possible. Additionally, there was no such relationship for GSTT1 or GSTP1 variants [4]. However, the two other studies suggest moderately significant association of prostate cancer risk with GSTP1105Val variant in populations of African descent and patients from Slovakia [3, 5]. It is also important in these reports that there are no such associations for GSTM1 and GSTT1 variants. It should be noted, that in these studies were different populations, what can suggest the importance of more extensive analyses of given ethnic group, including greater number of cases and unification of the study group with appropriate choice of control group.

4. Summarize

The etiology of prostate cancer is still unclear, despite numerous studies and in many publications it is defined as multivariate, including both environmental and genetic factors. Interactions between them are also still not clearly defined. It is believed, that interindividual differences in susceptibility to carcinogens may be an important aspect

of prostate cancer's etiology, therefore in recent years this fact is the aim of many studies [4].
Despite the extensive analysis of the frequency of glutathione S-transferases, the enzymes important in detoxification of potential carcinogens were made, their role in the development of prostate cancer is still not clearly defined. Meta-analyses of this subject are contradictory [1, 12], while further clinical studies show different correlations of GSTM1, GSTT1 or GSTP1 polymorphisms with prostate cancer [3, 4, 5].
Presumably, non-compliance analysis results from diversification of study groups and different classification of person recruited to the control groups. It is also important, that complex etiology of prostate cancer cannot be caused by a single factor, and must be a measure of many interrelated factors [3].
The positive fact of the role of the GSTs in prostate cancer is their protective role in cancer chemotherapy, which may result from their lower enzymatic activity. This may have a beneficial effect in patients treated with chemotherapy, in view of the reduction of detoxification, which potentially increase the efficacy of a drug [3].
For understanding the role of glutathione S-transferases in prostate cancer we need further, multicenter studies, which will be concretised in terms of selection the unhealthy population and homogeneity of comparison group, what will clearly substantiate the correlation of antioxidant enzyme's activity with prostate cancer. It is also necessary to study not only the causality of a disease, but also the influence of definite defect on further course of the disease and its treatment to consciously try to alleviate its effect.

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