

The influence of xenobiotics and environmental selection upon carcinogenic changes in human male reproductive system

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ABSTRACT

This review is a compilation of the recent reports on a role of environmental factors on a cancer development in male reproductive system. We have analyzed studies of environmental pollution and disorders of mechanisms responsible for defense against impact of xenobiotics upon the prostate cancer and testicular cancer occurrence. Moreover, we have focused on the polymorphisms of selected genes, which in excessive exposure to environmental stress factors might exacerbate disorders of an organism defense against impact of xenobiotics. It is well known that environmental factors such as toxic heavy metals pollution, impact of xenobiotics or environmental stress have an influence on the human reproductive system. There were many studies suggesting an association between these factors and the prostate

or testicular cancer development, but still there are no unambiguous conclusive results. Studies of specific changes in markers, which occur in response to various environmental stressors are also very interesting. They focus on the influence of chemical elements (Cd, Zn, Ca) destabilization and heavy metals pollution over an organism and the environment. Antioxidant enzymatic mechanisms in conditions of anthropogenic impact and the influence of polymorphisms in genes involved in genetic material damage repair under stress conditions have also been studied. The aim of this review was to combine essential important data suggesting possible role of environmental factors in the initiation and development of carcinogenic processes in male reproductive system based on prostate cancer and testicular cancer cases. On this basis the current needs and research directions could be delineated.

INTRODUCTION

Due to the increasing number of male reproductive system disorders such as infertility, cancers or other diseases, many studies are conducted, trying to define the causes of this health problem. Some studies analyze the hypotheses of a significant influence of environmental factors on male genitals (Aitken et al. 2006; Myrup et al. 2008). Aspects of direct interaction of xenobiotics interactions and genetic background, in which these factors interact, were the main subject of research. Feasibility of those studies is confirmed by reports of unresolved impact of concrete chemical

elements, which are introduced into the body in the form of various bioactive chemical groups, both in polluted air, water, or with the food chain in natural environments and during diet supplementation (Fingerhut et al. 1991; Gao et al. 2005; Goyer et al. 2004; García Sánchez et al. 1992). The information about disturbed antioxidant enzymes status in the patients with cancer changes also do not give a definite answer. Similarly, in the case of repair genes polymorphisms, responsible for impaired synthesis and metabolism of proteins important in defending the body against xenobiotics, the conclusions are vague (Battisti et al. 2011; Ricks-Santi et al. 2010; Srivastava et al. 2005).

This review provides a basis to delineate current needs and direction of research in the discussed field of knowledge. This will allow to plan studies leading to explanation of possible multilateral interactions between exposure to varied environmental stressors and the increased incidence of male reproductive system cancers.

It is believed that environmental factors (excessive heavy metal pollution, influence of xenohormones, excessive stress) affect human reproductive system. Aitken et al. (2006) indicate an association between environmental xenobiotics and increased infertility among men in Australia. They also emphasize the increased incidence of testicular cancer in this country. Likewise, Myrup et al. (2008) study of Danish immigrant descendants confirmed the increase of cancer incidence in the next generations, living in the industrial regions. Recently possible environmental factors involved in prostate cancer pathogenesis have been investigated in several studies (Gao et al. 2005; Goyer et al. 2004; Ricks-Santi et al. 2010; Srivastava et al. 2005). Goyer et al. (2004) analyzed such factors like age, ethnicity, occupation, lifestyle and living environment upon complexity of prostate cancer. Furthermore, they have stated that the relation between genetic background and environment cannot be ignored. Studies of prostate cancer were focused on the impact on cancer by various chemical elements, mainly cadmium, zinc or calcium and also some other groups of elements in the environment (Fingerhut et al. 1991; Gao et al. 2005; García Sánchez et al. 1992; Goyer et al. 2004). Generally, to understand that impact of environmental stressors on cancers the research was focused on activity of enzymatic and non-enzymatic antioxidant mechanisms. The last reports (Battisti et al. 2011; Ricks-Santi et al. 2010; Srivastava et al. 2005) also focused on the gene polymorphisms, which could be responsible for increased male susceptibility to prostate cancer. These polymorphisms are located in genes responsible for the repair of damage caused by different environmental stressors. Similar clinical studies were conducted for patients with testicular cancer (Harries et al. 1997; Koizumi and Li 1992; Manecksha and Fitzpatrick 2009; Sabanegh et al. 2010). These studies confirmed so far an association of cryptorchidism, physical injuries, testicular atrophy and exposure to sexually transmitted diseases with testicular cancer etiology. Other scientists have also considered the combined role of environmental and genetic factors (Sabanegh et al. 2010).

THE IMPACT OF CHEMICAL ELEMENTS UPON CANCER OF HUMAN MALE REPRODUCTIVE SYSTEM

Carcinogenic impact of chemical elements and their influence on neoplastic lesions in the prostate are important from the view point of medicine and seminology. Numerous studies are related to the influence of cadmium and its compounds, e.g. cadmium is known as human carcinogen as it causes the increase of the risk of lung cancer and is

suspected to play a great role in the prostate cancer etiology. The previous results did not provide unambiguous information, despite the positive results in tests on rats (Goyer et al. 2004). Studies with animals show unusual dependence of prostate tumors formation, in which lesions occur only in rodents treated with the dose of the element below the threshold of significant toxicity in testes. It could be caused by essential importance of androgens production by testes, which is significant in prostate cancer maintenance. Androgens secretion by testes may be disturbed in the high toxicity and results in lesions just in testes, without maintaining lesions in prostate (Goyer et al. 2004). In human population studies, Potts (1965) and Elinder et al. (1985) showed significant associations between occupational exposure to cadmium and prostate cancer. However, Goyer et al. (2004) have noticed that there were many studies of occupational exposure reporting the lack or any significant associations thus this issue remains open. In the case of testes, experiments on rats conducted by Bialkowski et al. (1999) indicated cadmium contribution in promutagenic 8-oxo-2'-deoxyguanosine induction, through 8-oxo-dGTPase inhibition. Thus there is a possibility of the association of this chemical element with occurrence of neoplastic lesions in testes (Aitken et al. 2006; Goyer et al. 2004).

In the prostate cancer an influence of zinc supplementation was studied also. This chemical element is important for proper functioning of male reproductive system. Leitzmann et al. (2003) reported the increase in the prevalence of prostate cancer in men applying a high dose of zinc. It is possible that an excess of this element, preventing testes toxicity, maintains testosterone production, which favors prostate cancer development. Excessive intake of calcium was also studied and it suggests an association with the risk of prostate cancer. But there are still no conclusive results in this field up today. The reports of an association between the risk of cancer and multivitamins intake or exposure to dioxins were inconsistent as well (Fingerhut et al. 1991; Lawson et al. 2007).

ANALYSIS OF ANTIOXIDANT ENZYME IN MEN WITH REPRODUCTIVE SYSTEM CANCER

It has long been known, that oxidative stress, on which environmental factors have great impact, causes increased activity of antioxidants, which determine the state of intracellular homeostasis. When this activity is disturbed, the organism, not having adequate defense, could be exposed to damages, including even the changes in genetic material, resulting in cancer development (Agarwal et al. 2006). Studies of enzymes activity such as catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) were conducted for determination of antioxidant mechanisms significance in prostate cancer (Agarwal et al. 2006; Arsova-Sarafinovska et al. 2009; Battisti et al. 2011). The analysis of antioxidant vitamins C and E quantification

and 8-hydroxy-2'-deoxyguanosine (8-OHdG) concentration were examined. Battisti et al. (2011) showed reduced activity of catalase and increased activity of superoxide dismutase in patients with prostate cancer, compared to the control group of healthy individuals. Moreover, the vitamins C and E quantification in serum were reduced in persons with cancer. The cohort studies including patients from Macedonia and Turkey (Arsova-Sarafinovska et al. 2009) showed reduced level of catalase, similar to previously cited study, but the level of superoxide dismutase were lower in the case of patients with prostate cancer, than in controls. This analysis provided also the information about lower activity of glutathione peroxidase in the individuals from cancer group (Arsova-Sarafinovska et al. 2009). The study involving 8-OHdG level, examined the level of oxidative DNA lesions, did not give conclusive results because of underdeveloped research process (inadequate method of study). Therefore the authors concluded that their ambiguous data clearly indicated the lack of antioxidant balance, confirming the hypothesis of antioxidant stress influence on prostate cancer (Arsova-Sarafinovska et al. 2009; Battisti et al. 2011). In the case of testicular cancer, we can cite results of Koizumi and Li (1992) study, estimating antioxidant enzymes levels in rats treated with the compounds of cadmium. They indicate the possible initiation of carcinogenesis under the influence of these chemicals, through reactive oxygen species. In this study, the increased level of lipid peroxidation and H₂O₂ cellular production, with growth of glutathione peroxidase activity and reduction in glutathione reductase and catalase activity have been observed after exposure to cadmium (Koizumi and Li 1992). These data suggest the role of environmental stressors in the cancer development in testes, which is the basis for further study of antioxidant enzyme levels in men with this disease.

POLYMORPHISMS RESPONSIBLE FOR INCREASED SUSCEPTIBILITY TO PROSTATE CANCER

Prostate cancer studies detected that the role of genetic factors is also important. Scientists discovered many polymorphisms responsible for increased susceptibility to this cancer, and selected mutations of *CHECK2*, *NBS1* and *BRCA1* genes have been analyzed as markers. In testicular cancer, the attention is paid to SRY (Sex-determining region Y) gene mutations, which could be involved in this disease development. In addition, scientists are trying to find new, specific for a population polymorphisms, which could be a background of increased risk of tumors (Mittal et al. 2011; Srivastava et al. 2005; Tang et al. 2000).

The intensive studies of the glutathione S-transferase genetic polymorphisms (*GSTP1*) were also conducted. It is one of the main enzymes involved in carcinogens inactivation by biotransformation. Harries et al. (1997) developed PCR analysis, which facilitates the determination of incidence of variants in *GSTP1* locus, in which adenine or guanine could

be interchanged. The possession of lower activity form of enzyme may be a cancer risk factor, and in the prostate cancer such form of *GSTP1* has been found (Harries et al. 1997). In testicular cancer the increased incidence of lower activity allele of glutathione S-transferase homozygotes has been noted, but also drew attention to its possible association with patients' age. Despite unclear results, it is believed that changes in human glutathione S-transferase gene can be linked to incidence of various cancers (such as lung, prostate or testicular cancer). Mittal et al. (2011) studied polymorphisms of *p53* gene, which among its numerous regulatory function, is also responsible for DNA damage repair. They discovered that the variant in codon 72 of this gene causes impaired activity of protein, which could have an impact on development of the various types of cancers. The population of African descent (Ricks-Santi et al. 2010) was studied and showed possible association of this *p53* polymorphism with prostate cancer. However, other researchers interested in changes in codon 72, provided the conflicting results, which in different populations showed different dependence (Ricks-Santi et al. 2010). In the case of testicular cancer, Peng et al. (1993) provided information about the lack of mutation in *p53* gene in patients (Peng et al. 1993).

Analyzing cytochrome P450 1B1 association with prostate cancer Tang et al. (2000) noted the increase in the incidence of Leu432Val variant in the group of patients with cancer, compared to healthy controls. Their findings suggest that changed forms of enzyme may be involved in carcinogenesis in Caucasians. This change has not been studied in the patients with testicular cancer, which could be an interesting issue to pursue in the future studies of this cancer. The genes responsible for the susceptibility to breast cancer (*BRCA1* and *BRCA2*) have also been considered as a possible causative agent of prostate tumors. In this case, the conflicting results are also observed. Kirchoff et al. (2004) have found confirmation of hypothesis about the association between *BRCA2* and increased risk of prostate cancer. An influence of *BRCA2* mutation on prostate cancer has also been described by Agalliu et al. (2009), who showed additionally, that mutation of *BRCA1-185delAG* was associated with cancers classified to high level of Gleason scale (high 7-10 and low 2-6 Gleason score cancers). Taking into account an association of *BRCA1* and *BRCA2* mutation with various type of cancers (e.g. breast cancer, ovarian cancer, pancreatic cancer), it might be worth to look for this mutations in the patients with testicular cancer, in which that aspect has not been studied yet.

CONCLUSIONS

Etiology of prostate cancer, which in men is the second cause of death due to cancer, is still not well understood. Every year 200 000 men die, whilst only in the U.S. there are 190 000 new cases yearly (Ricks-Santi et al. 2010; Srivastava et al. 2005).

Despite good progress in knowledge of the origin of this disease, like an explanation of the role of testosterone, scientists are still trying to define both environmental and genetic factors increasing susceptibility to this cancer.

Another important cancer which affects men is testicular cancer, which shows increase in the recent decades in most countries. Its frequency is much rarer than prostate cancer comprising only 1-2% of all male cancers, but its occurrence is most prevalent in young men which is worrisome (Manecksha and Fitzpatrick 2009). Moreover, amongst its causes possible environmental factors were mentioned, which could be an issue for further studies.

Available literature data suggest the existence of interactions between exposure to environmental stressors and increased susceptibility to cancers, including male reproductive system cancers. Different chemical elements, which are introduced into the body may play significant role in this process. Perhaps the individuals with cancer will have changed antioxidant enzymes activity, responsible for their worse defense against carcinogenic factors. In turn, studies of some genes polymorphism may indicate the disorders of proteins, which are important for defense against xenobiotics. Perhaps the results of future studies will give us a new view on the cause of male reproductive system cancers.

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