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The process of cancer. Part I. The role of selected factors in the induction of carcinogenesis

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Summary

Introduction and objective: Cancer arises from genetic and epigenetic changes in the cell. Indication of the direct causes of cancer is no doubt very difficult, because the process of carcinogenesis is a multi-level and multi-stage. Knowledge of existing threats to health is a determinant in making everyday decisions that are crucial in minimizing the risk for precancerous and cancerous. Featured Review article is only an outline of selected factors participate in the induction of neoplastic process. Its aim is to present the concept and the process of carcinogenesis, and to discuss the participation of selected factors in the induction of neoplastic lesions.

Description of knowledge: Preiniciation is a period in which the carcinogenic effect on normal cells. Initiation is related to the appearance of the first permanent changes

in the genetic material of the cell. The promotion is the stage in which the diseased cells grow and multiply. However, in the progression of metastasis occurs it. Factors that are surrounded by human impact on the integrity of the genetic material. Many of them have been scientifically proven effect mutagenic and carcinogenic.

Conclusions: The effects of interactions of carcinogens accumulate in different time intervals. Carcinogens interact with DNA, causing deterioration or change in its structure. They can also cause changes in gene expression. Carcinogenic for a human body may be the same ingredients, food products and substances in food preservatives. Some viruses can be oncogenic due to the integration of the viral genome into the host genome in the vicinity of proto-oncogenes. Exposure to heavy metals and their metabolites contribute to DNA damage.

Keywords:cancer, carcinogenesis, carcinogens, exposure

Introduction

Tumors are, after heart disease, the second most common cause of morbidity and mortality worldwide. In 2016 in Poland, the number of new cancer cases amounted to about 180.3 thousand. Compared to 2014 there was an increase by 21.1 thousand. Forecasts indicate that in 2029 the total number of new cancer cases in Poland may reach over 213 thousand [1].

Cancer (lat. *neoplasm*) Is "an inherited disease which results in the cells lose control over their divisions, whereby an enhanced their proliferation. This leads to loss of not yet performed in the body the "[2]. It arises as a result of genetic and epigenetic changes in the cell. Most cells in the body is in a resting phase. Their indexing cycle begins with the effect of stimulating factors. This leads to uncontrolled division of cells of the body parts, which are then not correctly differentiate into specific tissue cells. In this process called carcinogenesis involving certain group of genes. The first consists of proto-oncogenes. Currently, there are about identified three types. They encode proteins corresponding to, among others, for monitoring the proper course of cell proliferation and differentiation. Due to mutation of proto-oncogene may cause the cells to neoplastic transformation and tumor growth. Damaged proto-oncogenes are called oncogenes. The second group of genes are the tumor suppressor genes, so.

antyonkogeny. Currently known, there are about 50, although the biological functions of many products of these genes are still undefined. These genes encode proteins responsible for the inhibition of cell division and growth. The best-known of this group of genes are genes TP53 and RB1. They are also called "guardians of the genome" (gatekeepers) as through recognition of DNA damage in cells expressing TP53. P53 protein encoded by the gene p53 plays a role in the human transcription factor which is responsible for induction of apoptosis in response to DNA damage. When it is not possible to repair damage, p53 gene initiates the process of killing the cell. Unfortunately, more than 65% of tumor cells is damaged in both genes. It should be noted that tumors do not arise from mature neurons or cardiomyocytes, and tissue whose cells retain the ability to divide. When it comes to repairing systems disorders, cell acquires feneotyp, which allows it to unlimited depth. In addition, it loses the ability to die. It becomes immortal. As a result of these changes is formed neoplastic proliferation [3, 4, 5].

Indication of the direct causes of cancer is no doubt very difficult. Genetic predisposition with environmental exposure on carcinogenic factors can lead to an imbalance between genes and proto-oncogenes supresowymi [3]. In addition, inappropriate lifestyle contributes to an increased risk of cancer. An estimated 70-90% of most human cancers are associated with behavioral factors, environmental and dietary [6]. Cumulative impact effects of carcinogens in different time intervals, until of cancer, explains the fact that the highest incidence of cancers recorded in the elderly. Sum of the effects of carcinogens, which act throughout life on human discloses likely with aging [7]. For this reason, it is considered reasonable approximation of the role of selected risk factors in the etiology and course of the process of carcinogenesis.

The process of carcinogenesis

Carcinogenesis is a multistage process in which there are four specific stages. They are: preinicjacja, initiation, promotion and progression.

Preinicjacja is a step which involves the interaction of carcinogenic agents on normal cells. Carcinogens by the International Agency for Research on Cancer (IARC-International Agency for Research on Cancer) is a compound or mixture of compounds that can initiate tumor formation or increase its recurrence [8]. You can be divided into two main groups. The first is genotoxic carcinogens, which are those that interact with DNA, causing deterioration or change in its structure. The second group is non-

genotoxic carcinogens which cause changes in gene expression without damage or transformation of the structure of DNA. They can also increase the sensitivity of the cells or tissues on the DNA derived from other sources [6].

The second step called initiation. It binds to permanent changes in the genetic material of the cell. Mutations that occur mainly in the genes encoding enzymes of DNA repair genesproto-oncogenes and tumor suppressor cause cancer transformation. In this step, a cell acquires the characteristics of a cancer cell and its ability to divide becomes unlimited [2, 9].

In the promotion stage of gene expression changes occur and clonal selection. Oncogenes are activated and increased synthesis thereof, which are intended to cause the growth and multiplication of cells [2, 10].

In the last stage are as phenotypic features of malignancy. Cancer cells proliferate and acquire the ability tometastasis. They can migrate to other organs through blood vessels and lymph vessels. In addition, this step increases the neoangiogenesis process, which results in the formation of new vascular connections for a better nutrition of the tumor [2, 11,12].

Mutations that occur in a healthy cell, leading to the initiation and induction of cancer in may be caused by three main carcinogens (biological, chemical and physical). To be biological agents include viruses, toxins, bacterial and parasitic, and hormones and free radicals. A group of chemical carcinogenesis causing the substances from cigarette smoke, exhaust gas, and some heavy metals. In this category are also contamination of food and drinking water. While the physical factors that increase the risk of cancer include mainly UV and ionizing radiation [2,4].

Factors and carcinogens associated with the consumption of food

Consumption of certain foods may affect the initiation process carcinogenesis. Carcinogenic nature of the foods is related to its primary components, added to the chemical compounds and the compounds which are formed in the subsequent process [13].

Aspartame (E951) is a synthetic sweetener. Methyl ester of L-asparagine-L-phenylalanine. In the human body it is degraded to aspartic acid, phenylalanine and methanol. Has a sweetness of 200 times sucrose, compared to [14]. It also has properties preservation and strengthening of fruit aromas. Due to the fact that to achieve an adequate level of confectionery product it should have a minimal amount

of the compound is used mainly in the production of dietetic foods and low-calorie, ie. "Light" [15]. The Cancer Research Center in Bologna were carried out research which showed that the increase in the incidence of leukemia and lymphoma may grow in proportion to the dose ingested aspartame. This may be formed by metabolism of aspartame methanol, which is converted to formaldehyde having carcinogenic effects [16]. Other research suggests that the consumption of aspartame above 50 milligrams per kilogram of body weight increases the risk of cancer. This is very important for people with a genetic predisposition to cancer, especially prone to the development of leukemia and chłonniaków [15]. In 2013, he again made the verification of the safety of aspartame. The results indicate that the substance is not carcinogenic and genotoxic. It was further found that in many foods naturally occurring metabolite of aspartame [17]. It should be noted, however, that the tolerable daily intake of this compound adopted by various organizations in the world are divergent. The results of research conducted on animal models suggest a link between aspartame and cancer illness,

Potassium nitrite (E249) and potassium nitrates (E252) are derived from nitric acid. Nitrite derived from nitric acid (III) HNO_2 and nitrate from nitric acid (V) HNO_3. The main task of nitrite in foods is inhibiting the growth of pathogens that produce toxin, commonly known as botulism. They also have antioxidant activity and improving the taste of the finished meat product [19]. While the nitrate (V) during long-term heat treatment and prolonged time of storage of products formed with food components hazardous to human health connection. Mainly it comes to connection with the decomposition products of amino acids, or secondary, and tertiary amines. As a result of this dangerous nitrosamines are formed [20]. Nitrosamines are mainly responsible for the induction of tumors of the liver, colon, pancreas, esophageal, tongue, kidney, lung and bladder cancer [21]. All nitrosamines are genotoxic, mutagenic, and carcinogenic tatarogenne [22]. They are found in smoked sausages, bacon, salami, ham, beef, hamburger, salted and smoked fish, processed fish [23].

Heterocyclic aromatic amines (HCA- *heterocyclic aromatic AMINES*) Are compounds of mutagens and carcinogens, which arise in the results of thermal food processing (roasting, grilling, frying, cooking). This applies mainly to products containing protein (beef, poultry, fish, pork). HCA act on these genes, which mutations are important in the development of cancer [24]. During the heat treatment of meat, the quantity of HCA is variable and dependent on time, temperature, type of meat and the method of preparation. The most HCA formed during a long heat treatment at high

temperature [25]. Studies using animal models have shown that HCA can induce among others liver cancer, stomach, lung, and leukemia. Tumors can also arise in the mouth, mammary gland, brain, colon and small intestine. Researches proves,

It should be noted that the HCA are also present in the air, cigarette smoke, rain water, smoke from combustion of wood and rubber, exhaust gas, municipal waste water, wine and beer [26.27].

Polycyclic aromatic hydrocarbons (PAHs), et al. polycyclic aromatic hydrocarbons (*polycyclic aromatic hydrocarbons*-PAH) are a group of organic compounds, the presence of which results from the incomplete combustion of higher hydrocarbons. They have strong genotoxic, mutagenic and carcinogenic [28]. Substances such as benzo [a] pyrene - B [a] P and 1,2,5,6-dibenzoanthracene, which are included to demonstrate particular properties of PAH carcinogenic nature. BaP is defined by the IARC as a major human carcinogen [29]. PAH are present in the exhaust gases, polluted air, cigarette smoke and grilled meat and smoked [8]. Furthermore, these compounds may contaminate the food by water, soil and air. Their presence has been detected in fruit and vegetables, so that the wax surface of the plant effectively takes PAH [30]. They are also in dairy products, which may be due to the livestock in the vicinity of roads of a city traffic [31].

Bisphenol A (BPA - bisphenol, 2,2-bis (4-hydroxyphenyl) propane) is an organic compound from the group of phenols, which is widely used mainly in [33]. It is used for the production of plastics (eg. Plastic bottles, food storage containers), and production of varnish covering the inside of the cans. It can also be found in cosmetics, toys, paper [34]. BPA has the ability to migrate to food products, therefore it is recommended to pay attention to the signs which are located on the product packaging. If there is no information regarding the absence of BAP ("BPA-free", "BPA free"), the packaging probably has them [35]. BPA disrupts endocrine effect, you might have to start signaling pathway in inflammatory breast cancer cells. This is associated with activation of MAPK kinase (mitogenactivated protein kinases), which indirectly affects the development of tumors of the breast tissue. Furthermore, the ability to mimic estrogen BPA ovary cells proliferate and increases the risk of tumor progression [36].

Other risk factors neoplastic process

Oncogenic viruses may contribute to cancer formation about 15-20%, via an effect on cell growth, changes in the cells resulting from long-term infection, and also as a result of disturbances in the immune system of man. Onkowirusa presence is not enough to develop cancer, but it increases the risk. The process of carcinogenesis induced by viruses is based on two basic mechanisms. The first is the insertion mutagenesis, which combines the viral genome into the host genome in the vicinity of proto-oncogenes. The second is the transduction of an oncogene, in which the oncogenic virus is a carrier [37]. For carcinogenic considered to mainly the following viruses: EBV (Epstein-Barr virus, Epstein-Barr virus), HBV (Hepatitis B virus, Hepatitis B), HCV (hepatitis C virus, hepatitis C), some types of HPV (human papilloma viruses, human papilloma viruses) [38]. EBV is a risk factor, among others, on Hodgkin's lymphoma, cancer of epithelial-lymphaticovenous stomach cancer, nasopharyngeal [39,40]. HBV and HCV increase the risk of a host of primary liver cancer. Likely to develop this cancer in infected compared to non-carriers of these viruses is estimated as 100 to 1 [41]. HPV increases the risk of cancer of the cervix, vulva, anus, penis, lung, head and neck, oral cavity, pharynx and larynx [42,43].

An important role in the induction process of carcinogenesis plays exposure to heavy metals and their metabolites which contribute to the formation of oxidative stress. This in turn results in DNA damage, which may lead to initiate thecarcinogenesis.

Elements such as arsenic (As), chromium (Cr), cadmium (Cd) and nickel (Ni) have been identified by the IARC as carcinogens with proven epidemiologically carcinogenic [7.44].

Arsenic is an element belonging to the group azotowców. It is absorbed into the body through the respiratory system and digestive tract. It is located mainly in air, soil, minerals, water, food and medicines [45] contributes to an increase in risk among skin cancer, liver, kidney, bladder and lung [46]. A study conducted by Polish researchers has shown that the higher the concentration of arsenic in the blood of the higher incidence of cancer. The study was conducted on a group of 1500 women from which more than 1100 women with elevated blood levels of As had developed about 100 different cancers. Most arsenic is in foods such as saltwater fish and seafood, cocoa and rice,

In the form of chromium as a chromate (VI) dichromates (VI) was found to be a factor mutogenny and carcinogenic. Toxicity of chromium (VI) results from the properties of its strong oxidation-reduction, which leads to modification of DNA. These compounds are used, among others, the production of other chromium compounds, agents for protecting wood, pigments for paints and varnishes. Particularly exposed to harmful chromium compounds are industrial workers [48,49]. Cadmium is toxic to the organism in any quantities, and can accumulate in the tissues. It located in contaminated food, especially in vegetables, cereals and [50]. In addition, it is used to produce, among others, different dyes, fluorescent paints, phosphate fertilizers or nickel-cadmium batteries. [51] Promotes the formation of kidney tumors, bladder and prostate cancer [52].

Nickel is found in nature, especially in soil and water. It enters the plant, and its concentration is highest among in spinach, soybeans, nuts and black chocolate. Nickel by causing the hypermethylation of the gene P16INK4A (belongs to the tumor suppressor) indirectly contribute to the impaired cell cycle progression, stimulating the proliferation and to induce tumor formation. Also reduces the functioning of the repair mechanisms of DNA fragments [53,54].

Summary:

1. The effects of interactions of carcinogens accumulate in different time intervals. The sum of the effects of the individual carcinogens discloses a high probability with age in the form of cancer.
2. carcinogens interact with DNA, causing deterioration or change in its structure. They can also cause changes in gene expression. Further increase the sensitivity of a cell or tissue on the DNA derived from other sources. Consequently, this leads to initiation and induction of neoplasia.
3. Most carcinogens has a strong property for the development of oxidative stress and production of reactive oxygen species. Free radicals destroy the structure of DNA. In addition, they alter the structure and function to modify proteins, resulting in inhibition of DNA repair mechanisms.
4. Carcinogens the human body may be the same ingredients, food products and substances in food preservatives. Further, the properties have carcinogenic compounds formed during thermal treatment of food. It is therefore necessary to limit the consumption of food marinated, smoked, grilled, deep-fried and canned.

5. Some viruses can be oncogenic due to the integration of the viral genome into the host genome in the vicinity of proto-oncogenes. The virus itself can also be a carrier of the oncogene.

6. Exposure to heavy metals and their metabolites contribute to DNA damage. This causes a reduction in the quality functioning of DNA repair mechanisms, which increases the risk to initiate the process of carcinogenesis.

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