HYGIENIC ASPECTS OF HUMAN CARCINOGENIC SAFETY WITH RESPECT TO BIOLOGICAL FACTORS

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Current approach to sanitary and hygienic measures in various parts of the national health care system should create new challenges aimed at practical prevention in the context of the safety of people from the environmental carcinogenic factors. The effective Russian SanPiN 1.2.3685-21 regulates hygienic requirements for the safety of environmental factors for humans; inter alia, the documents lists biological carcinogens and carcinogenic lifestyle factors. The efforts of sanitary specialists in general and employees of Rospotrebnadzor in particular aimed at prevention of harmful impact of the existing carcinogenic factors shall be more effective if the available information on the potentially dangerous biological agents of carcinogenesis is more complete. This paper reviews the modern sanitary and hygienic aspects of carcinogenic factors of biological nature, and describes the causes of oncological diseases caused by them as well as the respective prognosis. Viruses, bacteria and trematodes, whose participation in the occurrence and development of a specific cancer is an established fact, are posed as etiological agents of the carcinogenic hazard biological factors present for a human being.

Keywords: biological carcinogenic factors, viruses, bacteria, sanitary prevention efforts organization, oncological morbidity

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ГИГИЕНИЧЕСКИЕ АСПЕКТЫ РЕШЕНИЯ ПРОБЛЕМЫ ОБЕСПЕЧЕНИЯ КАНЦЕРОГЕННОЙ БЕЗОПАСНОСТИ ДЛЯ ЧЕЛОВЕКА ФАКТОРОВ БИОЛОГИЧЕСКОЙ ПРИРОДЫ

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Современная организация санитарно-гигиенических мероприятий в сфере различных звеньев отечественного здравоохранения должна создать новые вызовы, направленные на практическое обеспечение профилактической работы в отношении безопасности для человека канцерогенных факторов среды обитания. На сегодняшний день в Российской Федерации действует СанПиН 1.2.3685-21, регламентирующий гигиенические требования к безопасности факторов среды обитания для человека, в котором перечислены биологические канцерогены и канцерогенные факторы образа жизни. Вместе с этим для организации специалистами санитарной службы и прежде всего сотрудниками Роспотребнадзора эффективной профилактической работы в отношении существующих канцерогенных факторов необходима более полная информация о потенциально опасных биологических агентах канцерогенеза. В представленном обзоре приведены современные санитарно-гигиенические аспекты изучения канцерогенных факторов биологической природы, описаны причины генеза и прогноза развития обусловленной ими онкозаболеваемости населения. В качестве этиологических агентов канцерогенной опасности для человека факторов биологической природы в обзоре представлена характеристика вирусов, бактерий и трематод, участие которых в возникновении и развитии конкретного онкозаболевания является установленным фактом.

Ключевые слова: канцерогенные факторы биологической природы, вирусы, бактерии, организация профилактической работы санитарной службой, онкологическая заболеваемость

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Introduction and improvement of measures designed to organize prevention work aimed at ensuring safety of people from carcinogenic environmental factors is one of the priorities for the current Russian healthcare system in the field of preservation of health of the population. Set up competently by sanitary service and, above all, Rospotrebnadzor, the effective efforts arranging state control over the said safety should further improve sanitary and epidemiological well-being of the population [1–10]. Currently, within the framework of a holistic view of the problems of safety of people from biological and environmental carcinogens, SanPiN 1.2.3685-21 considers such as the indisputable triggers of existing and potentially dangerous conditions promoting the spread of malignant neoplasms (MN) [11]. At the same time, doctors of medical and preventive care organizations as well as sanitary service specialists face an increasingly growing number of cancer patients, with various carcinogenic environmental factors often being the causes of specific nosologies [12, 13]. The difficulties associated with an objective study of human safety from carcinogenic environmental factors necessitate an analysis of works systematizing the use of modern sanitary and hygienic knowledge and standards in the context of the current situation in the domestic health system [14, 15]. The developments related to prevention measures, designed to assess the degree of danger biological carcinogenic factors pose to humans, are topical for the hygiene science and have both fundamental and applied importance.

Sanitary and hygienic rules of safeguarding people from carcinogenic environmental factors: current legislation

The International Agency for Research on Cancer (IARC), which is part of the World Health Organization (WHO) system, considers studying carcinogenic environmental factors to be a global problem of our time. Currently, WHO notes that MN are on the rise, and predicts continuation of this trend: in 2022, there were 20 million new cancer cases registered in the world, and by 2050, the number will increase to 35 million per year. In the Russian Federation, there up to 600 thousand new MN cases reported annually. The cumulative risk of developing a malignant tumor, i.e., one caused by a combination of stressors, is 23%, that is, almost one in five Russians may suffer the onset of cancer every year. At the same time, according to the IARC experts, the overall MN morbidity risk decreases by full 70% when a person stops being exposed to carcinogens [14–19].

The long-term exposure of people to carcinogenic risk factors that promote development of MN obliges the environmental safety and hygienic services to take supervisory legislative decisions at the level of the state that are designed to safeguard the population from the said factors.

Moreover, reduction of the level of pollution is one of the priorities of the Russian state policy in the field of environmental protection, reflected both in Article 42 of the Constitution of the Russian Federation and in the Federal Law "On Environmental Protection" [20, 21].

Legislation is constantly appended with sanitary regulations designed to make living and industrial environments safe in general and in terms of carcinogenic hazards in particular. Article 2 of Federal Law 52-FZ of 30.03.1999 "On the sanitary and epidemiological well-being of the population" lists legal, organizational and other measures aimed at ensuring the sanitary and epidemiological well-being of the population of the Russian Federation [22].

SanPiN 1.2.3685-21 "Hygienic standards and requirements for safety and (or) harmlessness of environmental factors for humans" lists known carcinogenic substances and their maximum permissible concentrations; section VIII of this regulation also gives biological carcinogenic factors that pose a danger to the population.

Analyzing biological carcinogenic factors, one should note that 18% of MN are of infectious genesis. Section VIII of the mentioned SanPiN lists more viruses than any other biological carcinogenic factor, which, according to the latest data, cause about 15% of human tumor neoplasms [23, 24].

Hepatitis B and C viruses, being exogenous oncogenic viruses, not only trigger acute hepatitis that becomes chronic but also entail liver cancer. It is generally recognized that chronic viral infections caused by hepatitis B and C viruses remain the dominant risk factors for the development of hepatocellular cancer. According to the available data, over 50% of hepatocellular carcinoma cases are attributed to chronic hepatitis B virus infection. In 2019, approximately 820,000 people died from hepatitis B, mainly because of liver cirrhosis and hepatocellular carcinoma. Moreover, in such situations, hepatitis C virus is an additional carcinogenesis risk factor, especially for non-Hodgkin lymphomas; it also makes development of thyroid cancer twice as probable, and raises the possibility of occurrence of hepatocellular carcinoma 2.5-fold [25–27].

Human papillomavirus (HPV) can cause oncological diseases, primarily those affecting female population (cervical intraepithelial neoplasia, cervical cancer), and a rare skin disease, Lewandowsky dysplasia. The share of malignant tumors associated with HPV is 5%; 75% of them are localized in the genital area, 25% outside it. The latter include oropharyngeal cancer affecting the oral cavity (tongue, pharynx, and larynx), malignant tumors in the anal canal, and penile cancer. However, not all HPV strains are biological carcinogenic factors, only those of the high oncogenic risk types: 17, 19, 35, 37, 39, 43, 49, 55, 56, 60, 62, 63, 72. Of them, types 16 and 18 exhibit maximum oncogenic activity, triggering development of malignant tumors of the cervix in 95% of cases [23, 27–32].

Epstein-Barr virus (EBV), one of the most common human viruses, is very important among the biological carcinogenic factors. EBV is widespread in the environment; contracted by humans, it most often leads to the development of non-oncological infectious mononucleosis. However, EBV can also provoke oncological diseases: nasopharyngeal cancer (nasopharyngeal carcinoma), lymphoepithelial-like carcinomas in the stomach, esophagus, tonsils, salivary glands, thymus, etc., as well as various lymphomas, including a malignant tumor of B-cell lymphocytes developing in the lymphatic system and hematopoietic organs, the so-called Burkitt lymphoma [33, 34].

It is now generally believed that the long-term persistence of functionally active **herpes viruses** in the cells of a human body creates conditions for occurrence and development of the factors causing MN. Immune, hormonal and genetic triggers related to the imbalance of homeostasis play a significant role in the pathogenesis of tumors associated with the herpes virus. Thus, human B lymphocytes turned out to be the target cells for it, and infection of immune cells with herpes virus sharply ups the rate of chromosomal aberrations with translocation of chromosome sections, which indicates a carcinogenic danger [35]. Electron microscopic studies confirmed the link between this virus and a number of human tumors: cervical cancer, nasopharyngeal cancer, Burkitt lymphoma. It was also discovered that malignant tumors are mainly caused by the human herpes virus type 8, and they develop against the background of severe immunodeficiency. For example, it is known to cause the Kaposi's sarcoma, a malignant lung tumor typically registered in patients with immunodeficiency syndrome [19, 36].

Human T-lymphotropic virus (HTLV) is a representative of the genus of delta retroviruses (*Deltaretrovirus*). HTLV-1 is a type I human T-lymphotropic virus capable of causing rare cancers several decades after infection, including T-cell leukemia and T-cell lymphoma (developing in about 5% of the infected population). The pathogenesis of cancer is associated with the introduction of the HTLV-1 virus into T-cells, which, illogically, rearrange themselves to produce proteins that enhance proliferation of the virus, and block protective $CD4^+$ and $CD25^+$ T-regulatory immune cells, which ultimately translates into immunosuppression conducive to malignant cell degeneration [37–41].

Human immunodeficiency virus (HIV) can be HIV-1 and HIV-2, with both variants closely resembling each other. They weaken the T-cell immunity, but produce no genomic oncogenic effects. Embedding a section of viral DNA into the genome of an infected organism, HIVs destroy $CD4^+$ lymphocytes and thus promote the development of dangerous opportunistic infections, subsequently increasing the risk of cancer growth. HIV-1 is not only ubiquitous, but also has greater virulence and infectious pathogenicity. At the same time, HIV patients have a higher incidence of cancer and higher mortality rates compared to the general patient population [42–46].

Currently, due to the high incidence of oncological diseases like Kaposi's sarcoma, lymphoma, and cervical cancer in AIDS patients, these diseases are labeled AIDS-associated. HIV patients are likely to have tumors in lungs, oral cavity, anal canal, testicles, skin (including squamous cell carcinoma and malignant melanoma) [47, 48].

An ideal example of how bacteria trigger cancer, especially stomach cancer, is the infection caused by ***Helicobacter pylori (H. pylori)***. The microbe is contracted in childhood, and half of the world's population has it in the gastric mucosa throughout life; in 1994, the IARC classified *H. pylori* as a group 1 carcinogen [49]. *H. pylori* has motile flagella, which enable to effectively colonize gastric mucosa, something other bacteria are poor in. As a result, patients with *H. pylori* not only suffer lesions of digestive organs accompanied by chronic inflammation, but also have MN developing in them with clinical signs of cancer or a MALT lymphoma (maltoma), characterized by damage to the lymphoid tissue of the stomach [50–52]. Some strains of *H. pylori* have the *CagA* virulence gene that disrupts apoptosis in the epithelial cells of the stomach, which pays a major role in this process. The *CagA* is also called a carcinogenesis factor or the first bacterial oncoprotein [53]. An infection with CagA-positive strains of *H. pylori* increases the risk of oropharyngeal and oral MN, esophageal, pancreatic, colon and colorectal cancers [54–58].

Based on the epidemiological studies conducted in Southeast Asia that showed a link between cholangiocarcinoma and *Opisthorchis viverrini* and *Clonorchis sinensis*, IARC included these **liver trematodes** in the register of biological carcinogens. Trematodes are a subclass of obligately endoparasitic flatworms [59–63]. A human can be invaded by trematodes when eating raw fish, crustaceans or aquatic plants that have not undergone heat treatment and contain larvae of the parasite. Chronic invasions, accompanied by frequent repeated infections by *O. viverrini* and *C. sinensis*, lead to chronic inflammation with fibrosis of the bile ducts, damage to the hepatic parenchyma, and subsequent development of cholangiocarcinoma, a deadly form of cancer. Hepatic trematodosis caused by *Opisthorchis felineus* is a disease frequently registered in the endemic regions of Western Siberia of the Russian Federation, where chronic invasion of opisthorchiasis is common. Numerous experimental and clinical data yielded by studies focusing on the *O. felineus* trematode also point to its of carcinogenic potential [64, 65].

Schistosomes, one of the most dangerous among the 12 species of trematodes parasitizing the human digestive tract, are recognized by the IARC as group 1 carcinogens. In many endemic regions, these helminths are considered responsible for oncogenesis. Every year, the incidence of schistosomiasis worldwide can claim up to half a million human lives. Helminthiasis infection results from the penetration of fresh water larvae (cercariae) of ***Schistosoma haematobium*** through the skin and mucous membranes into human blood vessels. The most typical symptoms of the disease are dermatitis, fever, malaise, myalgia, abdominal pain, hemorrhagic diarrhea, hematuria. According to WHO, over 250 million people in the world need prevention of and treatment against schistosomiasis currently [66]. Becoming chronic, schistosomatosis contributes to the development of such diseases as squamous cell carcinoma of the bladder, cholangiocarcinoma, and hepatocellular carcinoma [67–70].

Sanitary and hygienic aspects of the prevention efforts aimed at safeguarding humans from biological carcinogenic factors

Currently, the biological factors listed in SanPiN 1.2.3685-21 and presented in this review (viruses, bacteria and parasites) are recognized by IARC as group 1 carcinogens responsible for oncogenesis contributing to the development of a number of MN [16, 71].

Most modern researchers claim that chronic inflammation is a common pathway for the occurrence and development of cancer, and oncogenes trigger oncopathology after activation caused by mutational changes in the genomes of somatic and germ cells as well as violations of immune homeostasis (inactivation of suppressor genes, etc.) [72, 73]. The induction of a chronic inflammatory process is accompanied by the biosynthesis of toxic and genotoxic metabolites, immune response impairments; it affects the composition of the host microbiome, ultimately leading to the progression of oncogenesis of various etiology [32, 74, 75].

For example, hepatitis B and C viruses, which cause acute hepatitis and turn into chronic inflammation, have been found to be the cause of liver cancer [26]. In patients with *H. pylori*, damage to the cells of the digestive organs is accompanied by chronic inflammation with the development of MN and clinical signs of cancer of the lymphoid tissue of the stomach. *O. viverrini* trematodes change the composition of the host's microbiome, which entails a cholangiocarcinoma [76].

Based on the above ideas, which determine the factors of biological nature involved in the development of cancer, preventive sanitary and hygienic measures designed to ensure carcinogenic safety can be outlined as a number of provisions:

– it is necessary to inform the population about the risks of oncological pathology associated with biological factors (viruses, bacteria and parasites) recognized by IARC as group 1 carcinogens;

– it is necessary to identify such factors and inform sanitary and medical professionals about them, monitor to detect biological carcinogens from the SanPiN in the environment and industrial facilities;

– it is necessary to timely diagnose infection with carcinogenic biological factors in various segments of the population;

– upon receiving information about epidemiological danger associated with a growing number amount of biological carcinogens, it is necessary to organize specific preventive measures in a timely manner;

– the number of persons who may be exposed to carcinogenic factors of a biological nature should be as limited as possible;

– it is necessary to organize therapeutic and preventive measures that limit the development of chronic inflammatory diseases under the influence of biological carcinogens;

– it is necessary to effect immunobiological measures aimed at vaccination against pathogens of hepatitis B virus and human papillomavirus;

– it is necessary for the sanitary service to organize multi-level oncogygenic education for general medical workers, oncologists.

CONCLUSION

SanPiN 1.2.3685-21 are of particular importance from the point of view of ensuring control over environmental factors dangerous for humans. In particular, this regulation focuses on countering the spread of carcinogenic lifestyle factors and the danger of contact with biological carcinogenic factors. Non-compliance with the rules set out by the SanPiN that concern interaction of the population with carcinogenic factors can lead to the development of a number of oncological diseases as well as extremely severe socio-economic consequences associated with the spread of this process. At the same time, the biological carcinogenic factors and carcinogenic

factors of the human environment listed in the SanPiN should be supplemented by several other dangerous contaminants found in the environment. There is preventive value in sanitary and medical professionals learning about the consequences of the presence of carcinogenic biological factors in the environment and at production facilities, such value allowing to create conditions for the timely implementation of health-preserving measures.

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