**PHYSICAL AETIOLOGICAL FACTORS IN TUMOROGENESIS**

**Epidemiological data indicate that prevention of several different tumors is possible**

In a certain percentage of cases, tumors occur regardless of exposure to environmental factors, mutations can never be completely avoided because DNA replication and repair processes are inevitably prone to errors. So if an individual were to live long enough, it is inevitable that at least one of his cells would accumulate enough mutations to become malignantly transformed. However, environmental factors can significantly contribute to the risk of developing a tumor, which is best demonstrated by comparing the incidence of tumors in different countries: for almost every type of tumor that is very common in one country, there are countries where that tumor is rare. Given that populations that have migrated have been observed to acquire the risk of developing tumors that are characteristic of the new country, it is considered that these differences in tumor incidence are determined mainly by environmental factors and not by the inheritance of specific genes. Based on the results of such studies, it was concluded that 80-90% of tumors can be prevented, or at least delayed. Unfortunately, different tumors are associated with different environmental factors and a population that avoids one risk factor is usually associated with another. There are certain groups whose lifestyle is associated with reduced mortality from tumors among people of a certain age. It is believed that according to today's conditions, one fifth of the population of Europe, or the United States, will die from tumors. However, the incidence of tumors among Mormons in Utah who avoid alcohol, coffee, cigarettes, and drugs is half as much as among members of the same group who also live in America but do not follow community rules. Although these data indicate that the occurrence of tumors can be avoided in most cases, it is very difficult, except for tobacco smoke, to precisely determine the specific environmental factors that are responsible for such large differences in the incidence of tumors in different populations, or to determine which the way they act.

However, several different classes of environmental factors have been identified that are associated with higher tumor incidence. And it's not just mutagens, but also the amount of food we eat, circulating hormones, irritations, infections, tissue damage

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| --- | --- |
| Cause | Tumor causative agent (calculated percentage in relation to the total number of tumors) |
| Tobacco smoke | 33 |
| Nutrition, obesity | 25 |
| Physical inactivity | 5 |
| Viruses | 5 |
| Alcohol | 3 |
| UV and ionizing radiation | 2 |
| Professional carcinogens | 5 |

**Sensitive Assays Can Detect Those Cancer-Causing Agents that Damage DNA**

Many quite disparate chemicals are carcinogenic when they are fed to experimental animals or painted repeatedly on their skin. Examples include a range of aromatic hydrocarbons and derivatives of them such as aromatic amines, nitrosamines, and alkylating agents such as mustard gas. Although these chemical carcinogens are diverse in structure, a large proportion of them have at least one shared property—they cause mutations. In one common test for mutagenicity (the Ames test), the carcinogen is mixed with an activating extract prepared from rat liver cells (to mimic the biochemical processing that occurs in an intact animal). The mixture is then added to a culture of specially designed test bacteria and the bacterial mutation rate measured. Most of the compounds scored as mutagenic by this rapid and convenient assay in bacteria also cause mutations or chromosome aberrations when tested on mammalian cells. A few of these carcinogens act directly on DNA. But generally the more potent ones are relatively inert chemically; these chemicals become damaging only after they have been converted to a more reactive molecule by metabolic processes in the liver, catalyzed by a set of intracellular enzymes known as the cytochrome P-450 oxidases. These enzymes normally help to convert ingested toxins into harmless and easily excreted compounds. Unhappily, their activity on certain chemicals generates products that are highly mutagenic. Examples of carcinogens activated in this way include benzo[a]pyrene, a cancer-causing chemical present in coal tar and tobacco smoke and the fungal toxin aflatoxin B1.

**Fifty Percent of Cancers Could Be Prevented by Changes in Lifestyle**

Tobacco smoke is the most important carcinogen in the world today. Even though many other chemical carcinogens have been identified, none of these appear to be responsible for anything like the same numbers of human cancer deaths. It is sometimes thought that the main environmental causes of cancer are the products of a highly industrialized way of life—the rise in pollution, the enhanced use of food additives, and so on—but there is little evidence to support this view. The idea may have come in part from the identification of some highly carcinogenic materials used in industry, such as 2-naphthylamine and asbestos. Except for the increase in cancers caused by smoking, however, age-adjusted death rates for most common human cancers have stayed much the same over the past half-century, or, in some cases, have declined significantly. Survival rates, moreover, have improved. Thirty years ago, less than 50% of patients lived more than five years from the time of diagnosis; now, more than two-thirds do so.

Most of the carcinogenic factors that are known to be significant are by no means specific to the modern world. The most potent known carcinogen, by certain assays at least, is aflatoxin B1. It is produced by fungi that naturally contaminate foods such as tropical peanuts and is an important cause of liver cancer in Africa and Asia. Except for tobacco, chemical toxins and mutagens are of lesser importance as contributory causes of cancer than other factors that are more a matter of personal choice. One important factor is the quantity of food we eat: as mentioned earlier, the risk of cancer is greatly increased in people who are obese. In fact, it is estimated that as many as 50% of all cancers could be avoided by simple, identifiable changes in lifestyle.

It is known that ionizing and ultraviolet radiation induce DNA damage, which can induce mutations, but all organisms have DNA preservation mechanisms (cell cycle control mechanisms, apoptosis). However, despite numerous protective mechanisms, not all cells fully restore normal DNA function and transform into malignant cells. Recently, we are exposed to new types of physical agents: radio waves, microwaves, electromagnetic radiation, nanoparticles.

Among the physical etiological factors, it has been proven that ionizing and ultraviolet radiation can cause tumors.

**IONIZING RADIATION**

Ionizing radiation is radiation that has enough energy to cause ionization of molecules by displacing electrons from atoms. Ionizing radiation can be electromagnetic (H rays and gamma rays) or corpuscular (electrons, protons, neutrons...). The first knowledge that radiation plays a role in the formation of tumors came about quite by accident. Namely, a few years after the discovery and application of X-rays for diagnostic purposes, a higher incidence of skin tumors was observed in professionally exposed health workers. A higher incidence of leukemia was also noted among radiologists and health workers who worked with radioisotopes. However, the most information was obtained after the atomic bombs were dropped on Hiroshima and Nagasaki at the end of World War II. Leukemias were the first malignant diseases whose growth was recorded already 3 years after the bombing. The highest degree of increase was recorded in the interval of 4-8 years after the bombing and gradually decreased in the next 20 years or so. The incidence of solid cancers increased somewhat later, but also lasted much longer, almost until today. Of course, it was immediately noticed that a predisposition was also necessary for the development of a malignant disease, since only a small number of those irradiated later fell ill with tumors. It is also known that the application of radiotherapy can lead to the formation of tumors. Thus, an increased incidence of hematological neoplasms was recorded in people suffering from ankylosing spondylitis who were treated with radiotherapy in the middle of the twentieth century, as well as an increased frequency of breast and thyroid tumors in people suffering from Hodgkin's lymphoma who were treated with radiotherapy.

**Biochemistry of radiation**

The interaction of ionizing radiation with living matter depends on the wavelength or energy. Shorter wavelength ionizing radiation has a higher energy that is sufficient to cause ionization of the molecules it hits. The target structure of the cell for ionizing radiation is the DNA molecule. Ionizing radiation acts on the DNA molecule directly, causing ionization of the DNA molecule itself, or indirectly, acting on water molecules from which free radicals are formed. The free radicals formed in this way have enough energy to ionize DNA molecules. Since free radicals are highly reactive, they can travel a short distance before interacting with the molecule, so it is necessary for them to settle in the vicinity of the DNA molecule in order to cause damage to this molecule. However, the conversion of reactive molecules that are created in the first moment can create hydrogen peroxide, which is weakly reactive and can persist longer and cause DNA damage even if it is distant.

Free radical scavengers normally present in cells such as glutathione can protect the cell. Even when the target molecule is ionized, the glutathione can protect the donating hydrogen atom and thus enables the pairing of the free radical atom with the hydrogen electron. This repair mechanism is the simplest and is called chemical repair. But if oxygen molecules are present, they will react with glutathione because they are in competition with free radicals, so the resulting peroxide cannot be chemically removed. Then the action of enzymatic repairs is necessary.

**DNA damage**

Regardless of whether it acts directly or indirectly, ionizing radiation causes damage to individual nitrogenous bases in the DNA molecule, as well as complete breaks in one or both DNA strands. Lesions occur in more than one hundred bases and sugar components of DNA. A cell in which damage to the genome has occurred tries to correct the resulting damage through the work of reparative enzymes. Often, genome damage is an irreversible change that leads to numerous mutations and chromosomal aberrations. This changes the expression and function of many proto-oncogenes and tumor-suppressor genes, which forms the basis of malignant cell transformation.

Protecting proteins from oxidation is also important, thereby reducing the percentage of oxidized enzymes that participate in DNA repair and thus there is a greater chance for DNA repair. It has been shown that one type of bacteria survives a high dose of radiation by affecting the activity of manganese, which protects enzymes from oxidation.

**Cellular response**

Proliferating cells are much more sensitive to the effects of radiation than resting cells. Cell cycle control points are activated in order to prevent the entry of cells with damaged DNA into proliferation. The most sensitive sensor of radiation-damaged DNA is the ATM kinase. Two ATM kinase substrates p53 and ChK2 are critical for cell cycle arrest. Deletions and mutations of the ATM and p53 genes are associated with the control of damaged DNA and the development of ataxia telangiectasia (Li-Fraumani) syndrome characterized by the appearance of tumors. By the way, the loss of function of the p53 gene was recorded in more than half of human cancers, so this fact was imposed as very important for considering the role of this gene in carcinogenesis. Mutations in the p53 gene are found in almost all types of human cancer, and the frequency varies among different types of cancer. These mutations are present in tumors of the bladder, esophagus, bones, colon, brain, cervix, liver, breast, larynx, lungs, hematopoietic cells, lymphoid tissue, ovaries, skin, pancreas, stomach, uterine endometrium, thyroid gland. Mutations of the p53 gene are particularly common in colorectal cancers (about 70%), lung (about 50%) and breast (about 40%).

**Radiation-induced cell death**

Terminally differentiated cells are more resistant to radiation than subterminally differentiated cells that are still dividing. However, non-dividing thymus and spleen cells are among the most sensitive cells, indicating that proliferation rate is not the only factor influencing radiosensitivity. Ionizing radiation causes cell death in different tissues by different mechanisms. First, p53-dependent and later p53-independent apoptosis occurs. Cell death caused by ionizing radiation can be associated with autophagy (cellular components are degraded in lysosomal vesicles). A problem related to ionizing radiation therapy is cell necrosis. Necrosis of healthy tissue can occur even months after ionizing radiation and be associated with an inflammatory response.

**Tissue sensitivity and latent period**

Although ionizing radiation can precede the formation of tumors of various tissues and organs, it is known that there is a different sensitivity of tissues and organs to the effects of ionizing radiation. Thus, ionizing radiation can easily cause the onset of acute and chronic myeloid leukemia as well as acute lymphoblastic leukemia, but so far there is no evidence that the occurrence of chronic lymphocytic leukemia and Hodgkin's lymphoma are related to the effects of ionizing radiation. On the other hand, among solid tumors, tumors of the thyroid gland, breast and lungs are most often associated with exposure to ionizing radiation. Somewhat less often, tumors of the colon, liver, esophagus, salivary glands, ovaries, bladder and central nervous system can be caused by the effect of ionizing radiation. On the contrary, there is currently no evidence that tumors of the pancreas, prostate, small intestine and cervix can be related to the effects of ionizing radiation.

It takes a certain amount of time to form a tumor after exposure to ionizing radiation. The period from exposure to ionizing radiation to the moment of tumor formation is called the latent period and is different for different tissues. The tissues with the highest proliferative activity show the shortest latent period. Leukemias appear already two years after the effect of ionizing radiation, while most solid tumors have a latent period of at least 5 to 10 years, and some even longer than 20 years. However, the length of the latent period is influenced by other factors such as radiation dose, age of the person, etc.

**Correlation between radiation dose and tumor**

Examining the connection between radiation dose and tumor formation is necessary for assessing the risk of tumor formation, especially when exposed to low doses of radiation. Accurate risk assessment is very important for regulating professional and diagnostic exposure to ionizing radiation. In support of this, there are several examples that require a more detailed discussion. One of the dilemmas is at what age should the use of mammography be introduced as a routine screening test for the early detection of breast tumors. The main dilemma is whether the benefit of early detection of breast cancer is greater than the risk of getting the same disease provoked by radiation during the application of this diagnostic procedure. There is an even greater dilemma regarding the use of computed tomography as a diagnostic procedure in children. Namely, the dose of radiation received during this diagnostic procedure is usually several times (sometimes 10-15) higher than the dose received during mammography. Taking into account the fact that the effect of ionizing radiation is greater in children than in the elderly population, as well as the fact that the dose of radiation is relatively large, the question arises very often and, of course, is justified, whether and when computed tomography should be used for diagnostic purposes in childhood.

Until now, there have been several theoretical models that tried to accurately determine the connection between the risk of tumor formation and radiation dose. One of them is the so-called linear-quadratic model. According to this model, when exposed to low doses of ionizing radiation, the existing risk of tumor formation shows a linear dependence with the dose, while at high doses, this dependence is a function of the square of the radiation dose. Otherwise, this model is based on numerous experimental results obtained during the exposure of experimental animals to different doses of radiation.

**Relationship between age and tumor**

The age of a person at the time of exposure to ionizing radiation is of great importance for the formation of tumors. Thus, it is known that the greatest risk for the formation of breast and thyroid tumors exists if the exposure to ionizing radiation was during childhood and the period of adolescence, while, for people over 45 years of age, ionizing radiation has almost no effect on the formation of tumors. It is believed that children and young adolescents are 10-15 times more susceptible to the effect of ionizing radiation on the formation of tumors than middle-aged and elderly people.

**Radiotherapy and oncogenesis**

People treated with radiotherapy, after many years (10 or more), show a higher frequency of so-called secondary tumors. Numerous studies agree that the risk of secondary tumors is higher in people who have received radiotherapy in the treatment of Hodgkin's disease, breast cancer, or when total body irradiation has been used as a pre-transplant preparation for hematopoietic stem cell transplantation. In principle, there are two types of tumors that arise as a consequence of the previous application of radiotherapy: sarcomas, which occur at the site of applied radiotherapy, and cancers in distant tissues and organs. However, in practice it is not quite like that. A higher frequency of bladder and rectal cancer was registered in prostate cancer patients treated with radiotherapy compared to prostate cancer patients treated with surgical chemotherapy. The use of radiotherapy in the treatment of Hodgkin's disease, especially if the disease is located in the mediastinum, is accompanied by a higher risk of cancer of the breast, stomach, thyroid gland, skin, acute leukemia and osteosarcoma.

**ULTRAVIOLET RADIATION**

Ultraviolet radiation does not have sufficient energy to cause ionization of molecules. Passing through living matter, ultraviolet radiation causes the excitation of molecules after the absorbed energy, whereby the molecules move into a more reactive state and enter into chemical reactions with other molecules more easily. Based on wavelength, there are three types of ultraviolet radiation:

**- wavelengths from 240 to 290 nanometers ("UVC");**

**- wavelengths from 290 to 320 nanometers ("UVB");**

**- wavelengths from 320 to 400 nanometers ("UVA").**

**Mechanism of DNA damage**

"UVC" and "UVB" achieve their effect by acting on DNA, there are changes in the position of double bonds, with the creation of pyrimidine dimers base (which often forms a cyclobutane ring) between two adjacent thimides on the same DNA chain and the so-called 6-4 photoproducts in the DNA molecule. These products interfere with the normal synthesis of DNA and RNA and have a mutagenic and carcinogenic effect. The distribution of changes in the genome depends on the nitrogen base itself, but also on the secondary and tertiary structure of the genome. Thus, cytosine absorbs ultraviolet radiation of a longer wavelength than thymine, so after exposure to UVB, cytosine dimers will be formed. The effect of "UVA" on living matter is achieved by the production of free radicals capable of causing DNA damage.

**Cellular response**

A nucleotide excision repair mechanism removes pyrimidine dimers and photoproducts. This pathway includes molecules that recognize changes in DNA, nucleases that cut DNA, and DNA polymerases that synthesize new nucleotides. Genetic disorders of these molecules are associated with the development of xeroderma pigmentosum syndrome, which is characterized by a 1000 times more frequent occurrence of skin cancer than in the general population.

UV radiation acting on proliferating cells activates both ATM and ATR kinases, whose substrates are p53 and ChK1, which cause cell cycle arrest in S or G2 phase. This radiation can also directly activate membrane receptors, causing their phosphorylation and transmission of signals that affect cell proliferation and apoptosis.

**Cell death**

UV rays induce apoptosis of skin cells, the mechanism has not been clarified, but it is believed that disrupted RNA synthesis due to the action of radiation is the main cause of apoptosis. Action on p53 can also induce apoptosis, although activation of this protein protects fibroblasts and keratinocytes from apoptosis. Cell death can also be induced by direct activation of FAS molecules by UV rays.

**Ultraviolet radiation and tumors**

Today, it is known that ultraviolet radiation is responsible for an increasing number of skin tumors. The amount of absorbed ultraviolet radiation, and thus the risk of skin tumors, depends on many factors: the thickness of the ozone layer, latitude, altitude, pigmentation, etc. Skin tumors are more common in areas with high insolation, as well as in people who are directly exposed to the effects of this radiation. Non-melanoma skin tumors usually appear on the head, neck and extremities, ie. parts of the skin that are directly exposed to the long-term effects of radiation. Pigmented skin is less sensitive to the effects of ultraviolet radiation. On the other hand, the appearance of melanoma tumors is usually not related to anatomical locations that are chronically exposed to ultraviolet rays, but the risk of the formation of melanoma tumors increases after acute burns caused by exposure to ultraviolet rays.

However, not all people who are exposed to long-term ultraviolet rays develop skin tumors. This means that there is a predisposition in the form of sensitivity to the effects of this radiation (an example is xeroderma pigmentosum, a condition that is characterized by accelerated aging of the skin when exposed to sunlight, ulcerations on the buccal mucosa and various neurological disorders, and these people have a great tendency to develop skin tumors). The occurrence of squamous cell and basal cell carcinoma of the skin is caused by long-term exposure to the effects of "UVC" and "UVB" radiation. Due to the formation of cyclobutane dimers in the DNA molecule and the absence of a reparative process, mutations occur in critical genes, which is the initial step in oncogenesis. One of the earliest events is the mutation of the p53 gene, and later additional changes occur in the genome. The development of squamous and basal cell skin cancer is accompanied by the appearance of specific and pathognomonic molecular changes in specific genes. On the other hand, the occurrence of malignant melanoma is associated with accidental skin burns caused by too strong sun rays. In contrast to squamous and basal cell carcinoma of the skin, in the development of which "UVC" and "UVB" radiation play a decisive role, malignant melanoma occurs much more often as a result of the effects of "UVA". The leading mechanism is the action of free radicals that cause irreversible damage to DNA molecules.

**MICROWAVE RADIATION**

Microwave radiation is radiation with a frequency between 300 MHz to 300 GHz, it does not cause ionization of the tissue it acts on, rather it turns into heat (the sources of this radiation are mobile phones, devices for wireless internet, kitchen appliances, radars...). There is still insufficient data on the effects of this radiation, but it has been shown that absorbed heat can subsequently induce the formation of free radicals and induce DNA damage in human spermatozoa in vitro. It also induces phosphorylation of the p35/MAPK pathway.

There are conflicting findings of various studies on the influence of microwave radiation on the development of tumors (there are data on the increased incidence of tumors in people who live near mobile phone transmitters or radio transmitters).

**ELECTROMAGNETIC RADIATION**

It does not directly cause DNA damage, but has been shown to interfere with DNA replication and thus induce cell apoptosis. This radiation also has non-genotoxic effects, it interferes with signaling pathways in cells, but the biological consequences of this effect are not yet known. There is a strong correlation between exposure to electromagnetic radiation and the occurrence of leukemias, brain tumors, and breast tumors.

**The use of mobile phones and the occurrence of tumors**

Mobile phones are a source of electromagnetic and radio wave radiation. Studies of the population that used mobile phones for 10 years indicated a higher incidence of brain tumors (acoustic neuroma and glioma) compared to the general population. The dose of radiation that the brain receives during a telephone conversation reaches values that cause DNA damage in laboratory conditions. However, there are studies that have not shown a positive correlation between the use of mobile phones and the incidence of brain tumors, but still, the time since the appearance of mobile phones is relatively short to still be able to draw a conclusion.

**ASBESTOSIS**

Asbestos is a natural silicate mineral used in woodworking. That exposure to asbestos is associated with the risk of tumor development was first confirmed in 1935. Asbestos fibers enter the cell and induce the formation of free radicals, especially in cells that contain a lot of iron. It causes DNA breaks and the appearance of 8-hydroxyguanine, chromosomal aberrations, and the appearance of micronuclei. Numerous signaling pathways in the cell MAPK, EGFR, NFκB are activated which induces inflammation, enhances cell proliferation, and increased expression of TGFβ stimulates fibrogenesis.

Epidemiological studies have shown that asbestosis increases the risk of developing lung and pleural tumors.

**NANOPARTICLES**

Nanoparticles are particles with a diameter of 1-100 nm. They are used for making paints, cosmetics, but also in medicine as carriers for delivering drugs to certain tissues. The cellular effects of nanoparticles are similar to the effects of asbestos, they induce the appearance of free radicals in the cell and inflammation. ATM and ATR kinases are activated, and nanoparticles induce the release of pro-inflammatory cytokines from the cell, TNFα.

The titanium dioxide nanoparticle used to make the paint is classified as a substance that may have carcinogenic potential. Although there are no data from epidemiological studies yet, this particle could increase the risk of lung and pleural tumors in the same way as asbestos.

**CHEMICAL ETIOLOGICAL FACTORS IN TUMOROGENESIS**

Back in the 19th century, it was noticed that chemical substances could be the cause of tumor formation, when an unusually high incidence of malignant diseases was observed among people who were professionally exposed to certain chemical substances. Later observations only confirmed the initial suspicions about chemical oncogenesis. Thus, Aksoy and his associates, in the period from 1971 to 1985, described in detail the role of benzene in the development of leukemia among workers in an Istanbul shoe industry where benzene was used as a solvent. Namely, the frequency of acute leukemia was almost 10 times higher among the workers in this shoe factory than in non-exposed persons. The change in the incidence of certain tumors among ethnic groups after migration, the significant increase in the number of malignant diseases among smokers, as well as among occupationally exposed persons only confirm the fact that the environment in which one lives and works, as well as the way of life can significantly change the frequency of certain types of tumors. Confirmation of the role of chemical etiological factors in oncogenesis was also obtained using numerous data from experiments on animals or in cell cultures.

Genetic predisposition is important for the formation of most tumors, but studies with twins have shown that the role of non-genetic factors is dominant. Therefore, for most tumors, exposure to chemical agents can be associated with tumor formation, and genetic predisposition increases the risk of tumor occurrence. Genetic factors influence risk by altering cellular defense mechanisms. Most human tumors are not ordinary, genetically determined, consequences of aging, but rather consequences of individual exposures (exogenous and endogenous) to other factors that enhance genetic predisposition.

**Types and mechanism of action of chemical carcinogens**

A list of over 200 chemical, physical and infectious agents associated with tumor development has been identified. Some of these factors are given in the table.

Within chemical classes, carcinogenic potential varies considerably among stereoisomers. Most chemical carcinogens are first metabolized and thus translated into an active form that reacts with DNA or alters epigenetic processes. As there is a good correlation between the ability of a chemical agent to form a covalent bond with nuclear or mitochondrial DNA and the ability to induce tumors in experimental animals, DNA is considered the main target of most carcinogens. Binding to DNA appears to be necessary but not sufficient for tumor development. Agents that act on DNA are classified as genotoxic agents.

Genotoxic agents can simply transfer a single alkyl- or aryl- group to DNA. This is how alkylating agents, aliphatic epoxides, nitroso compounds, polycyclic hydrocarbons and numerous food and mineral oil ingredients work. Other genotoxic carcinogens carry out the transfer of arylamine groups to the DNA molecule, and these are most often aryl-aromatic amines, aminoazides and heterocyclic aromatic amines, which mainly originate from thermally inadequately prepared food (overfried, burnt, overcooked meat and vegetables).

The binding of carcinogens to DNA is not random and each class of agent interacts with a specific purine or pyrimidine. In addition, the action of chemical agents on DNA is determined by the nucleotide sequence, DNA repair mechanisms. It follows that chemical carcinogens are mutagens that cause base-pairing errors, missense and nonsense mutations. Some can cause macrogenetic damage, such as chromosomal breaks and deletions. In any case, the changes detected in the tumor represent a combination of the effect of mutagenic changes on the function of the product of that gene (protein) and functional changes of the host cell (examples are p53 mutations in human liver tumors caused by aflatoxin, or in lung tumors caused by polyactyl aromatic hydrocarbons present in cigarette smoke).

Known or suspected chemical carcinogens

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| --- | --- | --- | --- |
| Organ | Agens | Industry | Tumor type |
| Lungs | Tobacco smoke, arsenic, asbestos, benzopyrene, beryllium, silk, 1,2-butadiene, chromium-IV compounds, tar, nickel, mustard gas | Aluminum production, gasification of gas, hematite mines, painters | Squamous, small cell, large cell, adenocarcinoma |
| Pleura | Asbestos | Inhalation, mining | Mesothelioma |
| Oral cavity | Tobacco smoke, alcohol | - | Squamous cell carcinoma |
| Esophagus | Tobacco smoke, alcohol | - | Squamous cell carcinoma |
| Stomach | Smoked, salty and canned food | Rubber industry | Adenocarcinoma |
| Colon | Heterocyclic amines, asbestosis |  | Adenocarcinoma |
| Liver | Aflatoxin, vinyl chloride, alcohol, tobacco smoke | - | Hepatocellular carcinoma, hemangioma |
| Kidneys | Tobacco smoke, phenacetin | - | Kidney cancer |
| Prostate | Cadmium | - | adenocarcinoma |
| Skin | Arsenic, benzopyrene, tar, mineral oils, cyclosporine, PUVA | Gasification of gas | Squamous cell carcinoma, basal cell carcinoma |
| Bone marrow | Benzene, tobacco smoke, ethylene oxide, antineoplastic agents, ciclosporin |  | Leukemia, lymphoma |

Some chemical agents that have been shown to cause tumors in experimental animals are not genotoxic. In general, the manifestation of their effect requires a huge dose and action over a long period of time. Many pesticides work in this way. The mechanism of action of these substances is still not reliably known. During their metabolism, many of them are a source of numerous free radicals that can damage target molecules in the cell. Others, on the other hand, can simulate the activity of hormones, thus influencing cell proliferation, differentiation and death.

Although the precise role of non-genotoxic agents in the development of human tumors has not been determined, they can nevertheless modify the activity of genotoxic substances by changing tissue homeostasis and thereby providing an environment for the expansion of the tumor clone.

Both geno- and non-geno-toxic agents can act on carcinogenesis through the induction of DNA and histone methylation or by acting on other processes involved in transcription. Permanent epigenetic change is an important factor in carcinogenesis.

**Animal models for testing chemical carcinogens**

Most human tumors can reproduce in experimental animals after exposure to a specific agent. In most cases, the origin of cells, morphological, phenotypic, genetic changes are identical to those occurring in human tumors. These models also indicate the constancy of host-ganes interactions among different mammalian species. Animal studies have shown that carcinogenic agents directly activate oncogenes, inactivate anti-oncogenes, and cause gene changes that are associated with autonomic growth and enhanced survival.

**Reparative processes in the cell and genetic predisposition**

The cell's capacity to repair DNA damage is enormous, protecting people from the accumulation of procancerous mutations so that most tumors are a disease of aging. Multiple perturbations in different DNA repair systems have been observed in individuals at increased risk of developing tumors. Mammalian cells with these disorders are susceptible to transformation after the action of chemical and physical agents.

DNA repair generally involves removing the DNA-carcinogen bond mainly on the strand that serves as a template for transcription to prevent the synthesis of the mutant protein.

Under the action of numerous methylating agents, highly mutagenic O6-methylguanine is formed, which is "repaired" by the activity of O6-alkyl-deoxyguanine-DNA-alkyltransferase, an enzyme that is necessary to prevent the formation of thymus lymphoma and colon cancer. Mutation of the gene encoding this enzyme predisposes to the formation of tumors. Other genes, such as BRCA-1, BRCA-2 and ATM, participate in the reparative processes of DNA molecules, so their expression disorders multiply the risk of breast, lung, liver and skin cancers (estimated up to 100 times). It is known that there is a genetically determined predisposition to the formation of tumors caused by chemical carcinogens. One of the most studied interactions is the impact of tobacco smoke on lung cancer. Genetic predisposition is a polymorphism (genetic polymorphism is defined as a gene variant that is present in at least 1% of the population) of the genes for glutathione-C-transferase M1, cytochrome P-450 1A1 and glutathione-C-transferase Pi, which are involved in the reparative processes of molecules DNA. Studies have shown that tobacco smoke causes hypermethylation of genes important for cell cycle regulation. The tumor suppressor gene p16 encodes the synthesis of a protein that is a cyclin-dependent kinase inhibitor, thereby blocking the transcription of cell cycle regulatory proteins. Methylation of this gene found in smokers is a predictive factor for the development of lung cancer.

**Chemical carcinogens and the risk of tumor occurrence in the human population**

People are often exposed to N-nitrosoamines and other nitro compounds that are found in food and tobacco smoke and are associated with a higher risk of developing tumors. Exposure to these agents can be endogenous through the synthesis of N-nitrosoamines from nitrates from food, cosmetics, drugs and tobacco smoke. The endogenous synthesis of these compounds takes place in the digestive tract through the conversion of nitrates into nitrites, and bacteria of the normal microflora of the digestive tract participate in this reaction. N-nitrosoamines are metabolically activated by cytochrome P-450 and form bonds with DNA.

Heterocyclic amines are produced by overheating foods containing creatine such as meat and fish, and are associated with the risk of breast and colon tumors (they are metabolically activated and bind to DNA). Aflatoxin causes liver cancer, but mainly if there is exposure to this toxin and infection with hepatitis viruses.

Aromatic amines play a role in the development of bladder cancer, especially in occupationally exposed groups (dye workers) and they require activation by cytochrome P-450.

Experimental and epidemiological studies have indicated the risk of hematological diseases, aplastic anemia, myelodysplastic syndromes and acute myeloid leukemia. Benzene is metabolized by cytochrome P-450 activity in the liver and converted to benzene oxide and hydroquinolone. Circulating hydroquinolones are further metabolized to benzoquinolones by myeloperoxidase activity present in bone marrow and leukocytes. Myeloperoxidase gene polymorphism is associated with a higher risk of developing hematological diseases.

**The relationship between tobacco smoke and oncogenesis**

The use of tobacco in any form leads to an increase in the incidence of not only malignant but also other diseases. Tobacco smoke contains more than 6,000 substances, of which more than 20 are known to be carcinogenic. First of all, there are polycyclic hydrocarbons, nitrosamines, aromatic amines, ethylene dioxide, 1,3-butadienes and others. In the last few decades, cigarette manufacturers have tried to reduce the level of certain carcinogens and nicotine, so cigarettes with a smaller amount of these ingredients are increasingly being used. However, the expected results were not achieved, given that smokers use these cigarettes in larger quantities. Also, the composition of tobacco smoke differs from classic cigarettes, so it is considered that this is the reason for the change in the frequency of the histological type of lung cancer (squamous cell carcinoma to peripheral adenocarcinoma). The risk of developing lung cancer is influenced by the number of cigarettes used during the day, the number of years of smoking, the type of cigarettes and the method of smoking (how deep the tobacco smoke enters the bronchial tree). We should not forget the genetically determined predisposition that is reflected in the metabolism of carcinogens, the repair of damaged DNA and the control of the cell cycle. Namely, only every tenth heavy smoker gets lung cancer, and many heavy smokers live into their 90s.

Lung cancer is not the only tumor that correlates with cigarette use. Today it is known that smoking is associated with the occurrence of cancer of the bladder, esophagus, kidney, larynx, pancreas, oropharyngeal region and stomach. In addition, tobacco smoke is indicated as a contributing factor in the development of acute leukemia, cancer of the liver, colon, cervix, prostate, gall bladder, etc. So far, no correlation has been found with the occurrence of brain tumors, Hodgkin's lymphoma, cancer of the skin, ovaries, testicles, etc. It has also been shown that quitting smoking significantly reduces the risk of numerous tumors.