Risk Factors and the Mechanism of Induced Oral Cancer by the Chemical Substances

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At this end of the millennium we witness an impressive increase in cancer frequency. According to WHO reports, cancer is the second cause of death, being overpriced by cardiovascular disease only. The oral cavity cancer is part of the ENT sphere malignant tumor group. It may appear at the level of any component structure: mobile tongue, mouth floor, retromolar trine (behind the last molar teeth in the lower arch), tough palate, internal cheek, lips, mouth vestibule or alveolar rebord. Salivary glands, although opening into the oral cavity, can not be included in this category, due to histological and enlargement features. Oral cancer is very easy to be noted because it causes a mouthstroke that does not heal over several weeks. This is the main symptom of the disease, but not the only one. Other signs are: whitish spots in the mouth, unexplained bleeding, difficulty in moving the jaw or chewing; hoarseness or considerable change in voice, loss of sensation or pain in the mouth, face or neck area, undue ear pain. The study includes 544 cases, and the statistical data collected over a 5-year period, 2013-2017, and: age, environment, sex, risk factors involved, location, tumor study and treatment are of interest. Combined therapy was reserved for patients with a low healing rate. The most common form of treatment was tumor removal within the limits of tumor safety, followed by another type of intervention: tumor extirpation and ganglion recording, whether or not associated with radiotherapy. An important role is also played by patients who come late, either due to a lack of health education or because of the fear of illness, or in most cases due to the oligosymptomatic character of the disease at the onset of onset.

Key words: malignant tumors, mouth ulcers, combined therapy, tumor removal

The first data on malignant tumors are related to the 15th century BC. Throughout the different historical epochs, doctors' concerns have been attracted to cancerous disease, the observations and assumptions about it being mentioned in various writings of the day belonging to Hippocrates , Galenus, Avicena.The increased frequency of cancer in the buco-maxilo-facial region is favored by a number of factors: the great diversity of maxillofacial structures and the very important changes in the course of phylogenesis and ontogenesis of these structures; the embryonic existence of the brachial arches, with the possibility of remaining remnants at this stage; the intense functionality of the face area of and of the oral region as the first segment of the matter import apparatus; (temperature, food hardness, dust, chemical poisoning, smoking, alcohol, sun rays, moisture, etc.)[1-3].

Disease has a serious impact on patients and sufferers, either through the infirmity created by the disease or its treatment, and by the often mutilation of sequelae. These consequences can be diminished if the disease is detected earlier, here interfering with the important role of the dentist through their knowledge of lesions with potential malignancy and the onset of signs of oro-maxillo-facial cancers through screening but and through the health education of the population. An important role also belongs to the patients who are late, in most cases because of the oligosymptomatic character of the disease in the onset stages[4-6].

In the oro-maxil facial area the localizations are as follows: face, lips and oral cavity, maxillary sinus, bones of the face (central intra-bone in the jaw and mandible); salivary glands (major and minor); soft sides of the face.

Excluding facial skin, a large majority are squamous cell carcinomas of the lips and the oral cavity (> 80%), the rest of the carcinomas and sarcomas develop in the salivary glands and the maxillary bones, but these are relatively rare (Johnson, 1991).

Oral and pharyngeal locations (in all statistics are grouped together) are ranked 6th in the world and third in developing countries.Epidemiological studies on oral cancer highlight the role indisputably played by factors favoring (risk) in its appearance and development: smoking (tobacco under all forms of cigarettes, snuff); betel chewing develops a fibrosis under the oral mucosa with malignancy risk in 4% -Murti); alcohol consumption potentiates the effect of tobacco; nutritional deficiencies (iron deficiency-Plummer-Vinson syndrome) cause atrophy of the basal membrane of the oral mucosa; fungal infections (Candida Albicans enzymes are able to develop carcinogenic chemical compounds by nitration-Krogh, Hald.Holmstrup); involvement of viruses in the occurrence of cancer: (Papilloma virus associated with cervical cancer, vulva, penis, esophagus, larynx (Kizuaba), Epstein-Barr virus associated with nasopharyngeal cancer, Burkitt lymphoma, lymphoma in immunodeficiency, Hepatitis B + carcinomas in the sick of AIDS), UV radiation important in the appearance of skin cancer of the face and exposed areas, especially in those with white skin. Also, they occur in the appearance of lip cancer; immunodeficiency (drug induced, HIV infection) provides patients with susceptibility

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to oncogenic viruses. The prevalence of oral cancer increases with age, however there is a country-specific difference and risk factors. Although the clinical examination of oro-maxillo-facial territory is extremely easy to perform, the oral cavity is accessible even for self-examination, although the patients are daily or repeatedly looking at lesions that grow on their face, lips, tongue etc. - because there are visible lesions. In all countries in the world and especially in developing countries, frequent cases call attention to the advanced stage of lesions (Gupta, Pindborg). Because of this, with all advances in the diagnosis, treatment and rehabilitation of patients, the survival rate at 5 years is 80% for lip cancer and only 30-40% for oral cancer (Binnie).The progress in cancer treatment refers to the reconstructive techniques that increase the quality of life, but not the survival rate (Meyers-Hankey, Son-Kapp, Silverberg-Lubera, Br andy). *Tobacco* is used for smoking for centuries, but its use dates back to millennia. When tobacco was introduced for the first time in Europe, smoking was recommended for medical purposes; but his value was quickly controversial. He was quickly condemned as a vice, one of the first opponents being James I. King of Great Britain who published anonymously in 1604 a treaty entitled *A Counter-Strike Against Tobacco*.

The spread of smoking is now the most widespread *epidemic* growth which continues its ascension on the basis of the multiple social roots of interdependence between people, whereby the generation of adult smokers can not avoid contamination of new generations who take up their knowledge before arming them with reason and will, knowledge of faculties necessary to avoid falling victim to vice[7-9].

Tobacco smoke, this *poison* with seductive qualities, repeating every day, every year, in the smoker's body often manages to worning out, to change the structure and normal function of the tissue elements it comes into contact with, to destroy the most important organs of the body.

Countless epidemiological and laboratory research, shows that tobacco smoke, one of the most extensive drug addicts, a true social scourge would kill four times as many people as traffic accidents per year[10-12].

The most *honest vice* as the practice of smoking was euphemized is just a slow method of self-destruction, ultimately suicide. WHO appreciates smoking as an instrument of death against which indifference can no longer be permitted.Cancer mortality, the most accurate indicator for the evaluation of this disease, is considerable higher in smokers compared to non-smokers, both with regard to cancers in general (all locations) and in particular some locations such as those exposed directly to smoking. Tobacco incidence in cancer, made quite sporadically in the past, chronologically followed manners different in consumption, namely, at the beginning, when the tobacco was snuffed, the cancer nose, then by using the pipe and the cigarettes, the cancer of the lip, and only later when the inhalation of cigarette smoke expanded bronchial cancer. Although the relationship between smoking and lung cancer in developed countries is the most researched subject in the history of medicine, there is very little specific information on the daily dosage of tobacco[13-15].

In the oro-maxilo-facial sphere poisonous stick or wand of death has been called a cigarette, can produce numerous morphological and functional changes: increased salivary secretion, altered salivary *pH*, decreased amylase percentage, calcium and potassium ions, increased saliva content of saliva, decreased oral number of bacteria, v (oral keratoses), leads to loss of natural color of the teeth, causes gingivitis, stomatitis, chronic periodontal periodontitis, fetisal halena, etc.

Tobacco and alcohol were the first etiological factors involved in the pathogenesis of the lip cancer since 1739. In 1795 Soemmerring involved pipe smoking as a cause of inferior lip carcinoma. The first large series of oral cancers in which tobacco consumption was predominantly predisposing factor was reported by Bouisson in 1859.

The lip cancer is included in many oral cancer studies, but reported separately, the number of reported cancers being small. However, three major case-control studies on lip cancer provide information about smoking. *The consumption of alcoholic beverages* is associated with the development of oral cancer in some patients. The difficulty in determining the influence of alcohol on the etiology of oral cancer lies in the fact that most people consuming excessive alcohol and smokes. In addition, it is difficult to obtain reliable information from patients on alcohol consumption. Last but not least, alcohol consumption varies greatly from one day to the next. Some people can make a *binge* while other people can consume a lot of alcohol a day.

A way that alcohol could affect the oral mucosa is its direct effect on cell membranes. If the oral mucosa is exposed to a solvent such as alcohol - removes some of the lipid components, the mucosa becomes considerably more permeable. This can help explain why alcoholics are at a much higher risk of developing oral and esophageal cancer[16].

It has been shown that ethanol (ethanol and water are the main components of alcohol) promotes the penetration into the oral mucosa of nitrosonornicotine from the tobacco substance being carcinogenic. The gastrointestinal system is exposed to a much higher alcohol concentration than other body tissues. Indeed, the intestinal epithelium contains alcohol-dehydrogenase, and therefore has the ability to metabolize alcohol. Alcohol-related injuries can therefore occur due to: the toxic effect directly to alcohol or carcinogenic compounds present in alcoholic beverages, the effects of alcohol metabolites - especially acetaldehyde or acetates; changes in cell redox potential as a consequence of alcohol metabolism[17].

In addition, chronic alcohol consumption can lead to salivary gland atrophy, and therefore salivary flow is reduced. Saliva has been shown to inhibit mutagenicity and clastogenicity. So a smaller amount of saliva can lead to an increase in oral mucosal exposure to carcinogens and thus an increased risk of oral cancer. Furthermore, they can be metabolites of alcohol that contribute to ethanol toxicity. Tobacco and alcohol are risk factors for oral cancer, although it has not been shown that pure ethanol is carcinogenic, it was concluded that the contaminating substances and its components are responsible for its association with cancer acting as an initiator. The independent role of both agents was demonstrating some authors suggesting that alcohol would have greater influence. However, the synergistic effect seems to be a much higher risk for oral cancer. Experimental studies have shown that ethanol is not itself a mutagen or carcinogen. Acetaldehyde, the first metabolite product, would have a mutagenic effect. However, in the current study of the theory of oral cancer, alcohol plays a role as a co-carcinogen, facilitating the development of the tumor or helping to develop it more than it would be the initiator itself.

Absence of *oral hygiene* is another common etiological factor of tumors oral cavity. In an oral cavity with no irritating mechanical, chemical, bacterial, etc., the incidence of cancer is considerably increased and vice versa.

Oral health is also dependent on oral septicity and the presence or absence of traumas. It is difficult to assess the influence of the infection on oral mucosa, but it is obvious that chronic intraoral infections are detrimental to the well-being of the oral cavity.

Bacterial proliferation products including bacterial toxins may have an irritant reaction that combined with other elements such as immunosuppression, nutritional deficiencies, alcoholism can increase the risk of malignancy. Tumor tissue is a current phenomenon and occurs in various ways. Mechanical trauma is probably the most common form of oral mucosal trauma, because the mucosal membrane is constant and directly in contact with harsh materials (tooth, prosthetic works, food).

We add countless habits such as biting, crushing, compression conscious or subconscious. Also, many harsh objects are introduced into the mouth in various customs and tics Thermal radiations also play an important role because many people consume food or beverages heated to temperatures that would not be skin-friendly either. Oral mucosa often shows erosions due to the effect of hot food. Various types of chemicals are introduced into the oral cavity resulting in inflammatory reactions. Unfortunately, many irritants, particularly aspirin and phenol, are recommended as topical remedies. According to this study, carcinomas are epidermoid-type in third-age patients (60-70 years) and appear in this context, contrary to common observations, as spontaneous tumors in which the only etiologically incriminated factor appears to be cellular aging and lesions oral mucosa with malignancy potential such as erosive planar lichen, leucoplasia, floral papillomatosis, etc. *Leucoplasia* is the most common precancerous lesion. The prevalence of leukoplasia appears to vary between 0.7 and 24.8% for the same people under observation, only changing the evaluation criteria used.The risk of malignant transformation was found to vary according to gender (higher among women) leucoplasia (longer in the case of idiopathic) long-lipped, or localized on the tongue / palate, presence of *candida albicans*, etc.

The prevalence of *erythroplasty* is not known, but is nonetheless less frequent than leucoplasia. The majority of case studies show an evolution to cancerous tumors or gallopian cancer, which has led most of the authors to conclude that this kind of precursor lesions have a high potential for subsequent malignancies. However, the role of erythroplasty as a precursor lesion in identifying early signs of *in situ* carcinogenic or gallopian cancer is far from being clear.

Oral submucosal fibrosis (OSF) is a chronic oral mucosal disease that occurs predominantly among the Indian population or occasionally among Asian peoples other than Indian.

Oral planal lice (OPL) is a mucosal dysfunction affecting 1-2% of the population. Its role as a true precursor remains unclear. The florial papilomatose of the oral cavity is a hyperkeratosis disorder characterized by fine, gray or rosy villities, or even vegetative and papillomatous masses, forming one or many well-defined plaques, slightly elevated with respect to the neighboring mucosa and detached from the normal mucosa, sometimes overlapping the planar lichen or the tabaccic keratosis. After a shorter or longer time these lesions turn in all the cases in the carcinoma epidermoid and verrucous carcinoma (Ackerman) rapidly metastatic.Oral cancer, according to research, is a result of a genetic mutation. There is an increased risk of oral cancer associated with exposure to mutagenic factors: tobacco and alcohol.

In programmed cell death control two oncogenes are involved: bcl2 and c-myc and the p53 protein. Oncogenes bcl-2 may action, not by stimulating the cellular proliferation and not even preventing the malignant clonas (such as Rb or p53) but by inhibiting the apoptosis of the cells in which it is expressed. The c-myc cognate is one of the keys to regulating cellular proliferation, paradoxically intervening, and in regulating apoptosis is observed when there is a decoupling between the high levels of c-myc expression and the disappearance of mitogenic signals.

Myc protein is a common step in the pathways for activating the death and multiplication of tumor cells; p53 would act as a guardian of the cellular genome. P 53 is a gene located on the p arm of chromosome 17 and is named because of the molecular weight of the protein encoded by it. Cancer is a genetic disease characterized by a sequence of genetic alterations essential to the development of malignant phenotype[18].

A typical feature of oral cancer is excessive proliferation of oral keratinocytes. Proliferation of keratinocytes can initially be limited only to the epithelial layer, resulting in a thin and disorganized epithelium. The key to understanding abnormal cell division in oral cancer is the replication of AND and the keratocite division. The active rays activate the Raf protein and other cytoplasmic kinases (MEK, MAPk) in a kind of arch. MAPk is the mutagen-activated protein kinase: Mek is the MAP kinase's kinase; RAF is kinase's kinase of MAP. Oncogene mutations can stimulate excessive proliferation of keratinocytes from oral cancer. The etiology of 70-90% of human cancers has been criticized for the intervention of environmental, physical, chemical, biological factors. Of these, *ionizing radiation* would only account for a minor proportion of total human cancers. The assessment of the carcinogenic risk of each chemical in humans is made taking into account the epidemiological and experimental criteria. It has been concluded that of the 422 chemicals, clusters of chemical substances and technological processes are considered to be risk factors for humans classified into three risk groups: carcinogenic sugars ,probable carcinogens ,possibly carcinogenic chemicals .

The general scheme of the chemical carcinogenicity mechanism

The current concept of the mechanism by which chemicals induce cancer can be synthesized in the figure below (Miller-1980).

The generalization is now accepted as the vast majority of chemical carcinogens are active only after metabolic activation in the body of electrophilic derivatives that initiates malignant transformation. Exceptions to this rule are made by alkylating and acylating chemicals that are electrophilic in their natural form, and can make chemical bonds with cellular macromolecules. Experimental data accumulated in recent years claim that the ultimate forms of chemical carcinogens are powerful electrophilic reactants. Thus, chemicals with so different structures come through metabolic activation in the body, active metabolites have a common electrophilic feature - so the last carcinogens contain in their molecules electron deficient atoms that can react with nucleophilic centers, i.e. with atoms possessing electrons capable of forming a chemical bond. Thus, the nucleophilic centers are found in the macromolecules such as nucleic acids AND, RNA (N,

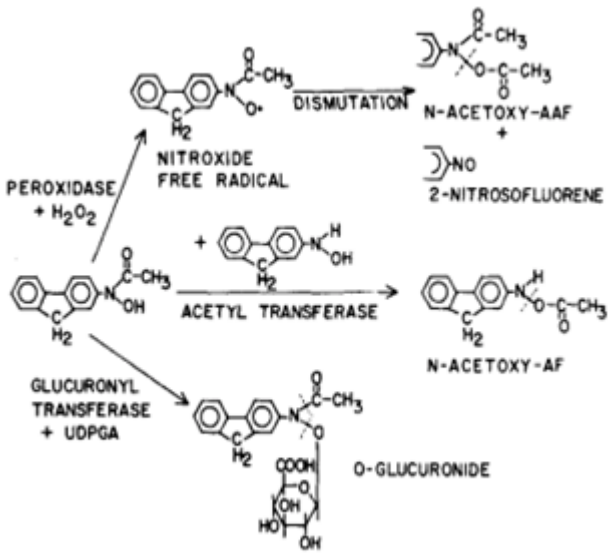

Fig. 1. General Scheme of Chemical Carcinogen . role of electrophiles in the initiation phase of carcinogenesis is observed

C, O) and proteins (with N, S, O). Miller et al. (1978-1980) were the first to show that biochemical activation of chemical carcinogens in the body is initiated by enzymatic systems, namely cytochrome P450-dependent oxidation in cell microsomes, systems similar to those that metabolize drugs and help to detoxify the body of harmful substances[18].

Lastly formed tumors, react nonenzymatically with nucleophilic centers. There is a possibility that a chemical carcinogen can give rise to more complexes with nucleophilic centers.

The stages of chemical cancerogeneses

It is now recognized that oncogenesis is a multistage process, determined by carcinogenic agents and influenced by tumor promoters, and comprises the following steps.The first stage has been called initiation, and it is irreversible, but can remain unsprung for a long time, so in a latent state. Changes produced at molecular level (AND) are structural, genetic.

The second stage of chemical carcinogenesis is promotion, which favors under certain conditions in the presence of promoters, the expression of changes in the first stage, after weeks or even months, years after initiation. Promoting can be reversed under certain conditions.

The intimate mechanisms by which tumor promoters act after binding them to specific receptors on the cell membrane are not fully elucidated. However, the effects of promoters on ion flux (Na +, Ca + +) are specified; on the metabolism of phospholipids and the induction of specific enzymes. At present, great efforts are being made to identify and specify complete carcinogens and promoters because prevention measures are different. Some data on the carcinogenicity of chemicals most commonly used in industry. Arsenic - Inorganic arsenic can cause skin cancer. Human exposure to asbestos in humans leads to an increased risk of aerobic cancers, etc.

It is assumed to have a potential contribution to the etiopathogenesis of oral cancer: viral agents, immune factors, diet and nutrition, and other risk factors.

Experimental part

Material and Methods

The study includes 544 cases and the statistical data collected over a period of 5 years, 2013-2017, and: age, environment, sex, risk factors involved, location, tumor study and treatment of patients with epidermoid carcinomas of the oral cavity and treated in the Oro-Maxillofacial Surgery Clinic .

Results and discussions

Out of the 544 patients, 83.9% were men, compared to women who occupied only 16%. While the number of patients per total is this, the tendency is not increasing and the female sex on the contrary, their number is decreasing.The most interested are people aged 60-70 years.

80% of the patients were from the rural area, and this explains the high share of basic carcinoma in men working in agriculture that are permanently exposed to sunlight.

As factors of risk found in the 544 patients studied are included smoking 54.4%; smoking and alcohol - 25.3%; only 20% did not find any risk factor. The most common anatomical-clinical forms were basal carcinomas and oral plans, followed by toague. We were considering the post-therapeutic TNH stage based on clinical classification (1987) and the anatomopathological examination of the operative part. The most frequent stages were III and IV followed by Stage I and II. A net increase in Stage IV weight in recent years was also explained, due to both the aggressiveness of the disease and the low socio-economic and educational level of the patients.

The treatment was multimodal and complex depending on the tumor stage and the anatomoclinic form, the general condition of the patients. Combination therapy was reserved for patients with a low rate of healing. The most common form of treatment was tumor removal within the limits of tumor safety, followed by another type of intervention: tumor extirpation and lymph node, whether or not associated with radiotherapy. Since oral cancer has increased over the last few years a great deal of surgical treatment, methods of treatment have diversified.

Conclusions

Epidemiological studies on oral cancer highlight the indisputable role played by factors favoring its development and development: smoking, betel chewing, alcohol, nutritional deficiencies, fungal infections, viral, ultraviolet radiation, immunodeficiency, etc. Oral cancer has a serious impact on patients and their families, either through the infirmity created by the disease or its treatment, and by the often mutilant character of sequelae.

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