UNIVERSITY OF MEDICINE AND PHARMACY
CRAIOVA

DOCTORAL SCHOOL

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ABSTRACT

CORRELATING ENVIRONMENTAL FACTORS
WITH
DIGESTIVE CANCERS

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Key words: cancer, indicators, incidence of digestive cancers, risk factors.
STATE OF KNOWLEDGE

CHAPTER I. INTRODUCTION

According to statistics and epidemiological data, contemporary period is dominated by an increased incidence of malignant tumors with various localizations, including digestive.

As a significant segment of pathology, malignant tumors at various sites, is a major problem of public health, with a major impact on the population. According to statistics published by Eurostat, both in European Union countries and in Romania, cancer is the second leading cause of death [1]. Specific indicators of mortality, morbidity, incidence or prevalence alongside social and medical size, high costs and delayed cancer diagnosis, are defining elements that emphasize the importance of studies of these disorders.

Researching environmental factors identified as risk factors for individual, community or population, can elucidate the mechanisms through which they can limit or facilitate a specific action on the human body.

CHAPTER II. DIGESTIVE CANCERS EPIDEMIOLOGY

Cancer is currently one of the most complex problems of contemporary medicine.

Oncological epidemiology cannot efficiently act by itself. Its main purpose is to investigate the causes of the emergence and development of cancer, by assigning a suspect etiologic factor with a certain type of cancer for our research with a particular location in the digestive sphere.

According to data published by the International Agency for Cancer Research on World Health Organization (WHO) - GLOBOCAN 2012: Estimated incidence, mortality and prevalence worldwide in 2012, cancer mortality is permanently increasing in the last two decades.

Digestive tract cancers represent approximately 20% of all visceral cancers and causes 25% of deaths from cancer, increasing in steady growth frequency for several decades, especially in countries with increased socioeconomic level.

Relevant to our research is the data from Table 1, where it can be seen that the specific mortality by malignant diseases in our country had an increasing trend in recent years.
higher than the European average (EU 27). The 221.6 deaths / 100 000 inhabitants is actually 1/5 of the total deaths ie 18.3% compared to the EU27 to 257.8 deaths / 100,000 cancer is 1/4 (26.7 %).

**Table 1. Specific mortality 2010 - leading causes of death in Romania and the EU 27 (deaths per 100 000 inhabitants, source Eurostat)**

<table>
<thead>
<tr>
<th>Region</th>
<th>Cardiovascular disease</th>
<th>Neoplastic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Romania</td>
<td>729.4</td>
<td>221.6</td>
</tr>
<tr>
<td>UE 27</td>
<td>378.3</td>
<td>257.8</td>
</tr>
</tbody>
</table>

**CHAPTER III. DIGESTIVE CANCERS ETIOPATHOGENY**

Epidemiological studies, experimental and clinical studies have led to the identification of a large number of causative factors of cancers including digestive disorders. Depending on their nature, they can be divided into:

- Exogenous: from the environment (responsible for 90% of human cancers)
- Endogenous: own body itself - genetic, immunological, endocrine and metabolic.

Among the 55 determinants of health indicators in the segment are a number of factors involved in neoplastic etiology, including digestive location: risk factors and protective factors (Table 2).

**Table 2. Risk and protective factors, specific of malignancies etiology**

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Protective factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental factors</td>
<td>Dietary fiber</td>
</tr>
<tr>
<td>Behavioral factors</td>
<td>Catalytic nutrients (vitamins and minerals)</td>
</tr>
<tr>
<td>Constitutional factors</td>
<td>Phytochemicals</td>
</tr>
</tbody>
</table>

According to data published by the Harvard Center for Cancer Prevention (HCCP) in Table 3 is show the majority of deaths attributed to cancer risk factor. We mention that among them there are also risk factors investigated as part of the etiology of digestive cancers.
### Table 3. Share deaths attributed to cancer risk factor (source Harvard Center for Cancer Prevention)

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>% Total deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food and Obesity</td>
<td>30%</td>
</tr>
<tr>
<td>Smoking</td>
<td>30%</td>
</tr>
<tr>
<td>Sedentariness</td>
<td>5%</td>
</tr>
<tr>
<td>Occupational factors</td>
<td>5%</td>
</tr>
<tr>
<td>The existence of cancer in relatives I°</td>
<td>5%</td>
</tr>
<tr>
<td>Viruses and other biological age</td>
<td>5%</td>
</tr>
<tr>
<td>Growth Factors</td>
<td>5%</td>
</tr>
<tr>
<td>Reproductive factors (sex hormones)</td>
<td>3%</td>
</tr>
<tr>
<td>Geophysical factors</td>
<td>3%</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>3%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>3%</td>
</tr>
<tr>
<td>Environmental pollution</td>
<td>2%</td>
</tr>
<tr>
<td>Ionizing radiation and UV sites</td>
<td>2%</td>
</tr>
<tr>
<td>Drugs</td>
<td>1%</td>
</tr>
<tr>
<td>Food Additives</td>
<td>1%</td>
</tr>
</tbody>
</table>

**Esophageal cancer.** Characteristic for adenocarcinomas is reflux gastroesophageal disease correlation with body mass index of the patient. This histopathological genre has an increasing incidence of esophageal cancer and represent about half of esophageal cancers. The main risk factors of squamous cell carcinomas are exogenous namely smoking and excessive alcohol consumption.

**Gastric cancer.** Malignant tumors gastric localized represents one of the most common cancers of the digestive tract. The causes gastric cancer are not well defined. Since this is a cancer of the digestive tract, diet was the risk factor most intensively studied: low consumption of fats and proteins; eating meat or salted fish; increased consumption of nitrates; diet poor in vitamins A and C.
**Colorectal cancer.** External risk factors of colorectal cancers are multiples:

1. **Obesity.**
2. **Diet:** Diets rich in vegetable fiber and low in fat may reduce the risk.
3. **RCC.** Increased consumption of fats, refined carbohydrates are associated with an increased risk.
4. **Calcium deficiency:** 1.25-2 g daily consumption of Ca $^{2+}$ was associated with a reduction in risk of recurrent adenomas (randomized).
5. **Micronutrient deficiency:** deficiency in folate, vitamin E and D increase the risk of RCC.

**CHAPTER IV. THE IMPACT ON HUMAN HEALTH CAUSED BY ENVIRONMENTAL FACTORS, SPECIFIC TO DIGESTIVE CANCERS**

Risk and protective factors in the environment, specific for digestive cancers are of major importance for understanding the current opportunities for identifying disease-risk groups of the population. The view that environmental agencies are the main cause of human cancers is derived from epidemiological observations.

*Specific risk factors of digestive cancers: “Lifestyle factors”*

**Nutrition.** The fundamental problem concerning nutrition is to maintain a balance between proper metabolism of each body and intake of nutrients from food. The concept of a balanced diet should be seen as a scientific way, by which the diet to become more of a protection factor than one of risk for the human health.

**Overweight. Obesity.** One aspect of current scientific interest is the overweight diet to related nutritional status that implies caloric consumption over the body's energy needs. It is not certain whether the three energy producing nutrients (proteins, carbohydrates, lipids) brought by food intake were potentially carcinogenic themselves or their unbalanced eating (perhaps in both senses), is a risk factor for colorectal neoplasia. Prospective studies show a link between obesity and colorectal cancer, considered a modulating factor of disease development. Obesity is Also Another modulating factor for development of colon cancer. Thus, the increase in body mass index (BMI) increases the risk of developing the disease. Current epidemiological studies show that the disposition of abdominal obesity is a better predictive factor than elevated BMI.

**Dietary fat.** By correlating the results of several studies it has been shown that reducing dietary fat consumption entails reducing the incidence of colorectal cancers. Lipids, during thermal processing undergoes a series of transformations resulting in compounds that can
have carcinogenic potential. Excessive consumption of fat associated with the protein leads to the development of the body of substances that can initiate the excessive proliferation of epithelial cells that will develop into colon mucosal dysplasia. Oxidative stress consequence of lipid peroxidation of unsaturated fatty acids is associated with colorectal carcinogenesis and the development of oxidative-antioxidative disorders lead to the disease's progress. Also, eating foods rich in animal fat, especially red meat and eggs is associated with etiology of colon neoplasia.

**Polycyclic aromatic hydrocarbons (PAHs).** Routes of exposure include air, water, food, skin contact and vocational subjects. The main route is the food intake demonstrated in human exposure to benzo(a)pyrene and to investigate metabolic pathways of these chemical carcinogens by colic mucosa, most studies have used human cell lines of type Caco-2; HT-29; HT-116; SW-486. Considering the lipophilic character of PAH, it has demonstrated a positive correlation between plasma levels of benzo(a)pyrene's and BMI by decreased response to the action of epinephrine (inhibition of lipolysis), which supports the hypothesis that PAH and obesity are modulating factors of colorectal cancer. Although they are substances naturally present in plant foods PAHs are present in many household foods. This may be due either to the transformation of nutrients (carbohydrates, proteins, fatty acids, cholesterol or carotenoids) during thermal processing of foods at temperatures above + 350º C like the preservation of food by the process of smoking, especially by the traditional technique that uses warm smoke. Modern technique of industrial preservation smoking uses liquid smoke or cold smoke.

**Nitrosamines (NOC).** These are formed by the reaction of secondary nitrosating pH-acid amines in foods with agents such as nitrates, nitrites and oxides of nitrogen (used as preservatives, especially meat and fish) in the presence of substances such as pyridoxine thiocyanates, some metals or alcohol. Nitrosamines are exogenous in a number of food: beer, fish and fish products, but also in meat and cheese. Nitrosamines are among the few carcinogens that can also be synthesized chemically or biologically catalyzed. The research of the effect of red meat consumption (more than 600g / day), has found that the NOC faecal is similar to that of smokers. This supports the hypothesis of the role of KRAS oncogene activation NOC in colorectal carcinogenesis involved in.

**Acrylamide.** These are potentially carcinogenic substances; food and cigarette smoke is the main source of exposure. After thermal processing of the food (above 120° C), asparagine (non-essential amino-acid) in carbohydrate-rich vegetables (potato, cereals) is converted to acrylamide. WHO recommends proper studies to estimate dietary exposure.
Alcohol and tobacco. Excessive alcohol consumption can cause important metabolic and immunological disorders. Toxicity is enhanced and referred to as the present substance in alcoholic beverages such as methyl alcohol, phenols, nitro-compounds, heavy metals, hydrocarbons or additives for preservation. The study's hypothesis is that alcohol can act as antifolate with altered methylation reactions and methionine metabolism whose role has already been proven in the process of carcinogenesis. Tobacco contains at least two secondary amine or pyrrolidine, and piperidine. During smoking, this is dissolved in the saliva and in the stomach once they are converted to nitrosamines, whose role in carcinogenesis has been previously discussed. There is currently an antismoke offensieve, most research demonstrating the role of this habit in the appearance of several types of malignant tumors. Epidemiological studies have demonstrated the link between smoking and colorectal cancer, 7,000 deaths per year are attributed to the United States of America.

Protective factors. Dietary fiber. Indigestible polysaccharides form with the lignin dietary fibers. Their physiological roles are multiple and beneficial for the human body: modifies intestinal transit time, regulates defecation, favors the development flora fermentation and cholesterol-lowering but the effect of supporting their role in colorectal cancers protection is the effect of absorption of toxic substances or potentially carcinogenic ones. Antioxidants. A number of foods serve to prevent colon cancer by their content in the antioxidants knowledge that neutralize free radicals and peroxides and represents a general mechanism of protection. Vitamins, mineral and biologically active substances (phytochemicals), in food, have multiple protective effects: antioxidant and antimutagenic (retinoids, lycopene, lutein, selenium); blocking the conversion of nitrites into nitrosamines (ascorbic acid and tocopherol); detoxifying enabled cellular metabolism (group B vitamins). Dietary calcium and dietary fiber reduces the activity of ornithin decarboxylase, which has a role in the initiation of mitotic process.

Other potential protective factors currently investigated are: cumarins, lactones, glutathione, ellagic acid, quercetolul, resveratrol, triterpens and others.

PERSONAL CONTRIBUTIONS

CHAPTER V. MOTIVATION AND STUDY PREMISES

Observational study named “Linking environmental factors with digestive cancers” was conducted by collecting data that were retrospectively analyzed and were aimed at
highlighting issues epidemiological and etiological related morbidity of this heterogeneous group of cancers in Dolj County. Analysis of risk factors linked to the analysis of environmental indicators of morbidity and mortality at the population level is a real need which the phenomenon is correctly assessed in detail and can substantiate establish health programs.

CHAPTER VI. MATERIAL AND METHOD

The research was conducted by retrospective - longitudinal study, for a period of 10 years, between 2002-2012, in the representative county of the South-West Oltenia, Dolj respectively. The data used in statistical interpretation were obtained by observing the two types of specific reporting sheets respective, sheet statistic for the cancer patient and the patient cancer record sheet (ONC1, ONC2). The last type of document review was periodically monitored due to findings of previous studies conducted in the Medical Oncology Clinic, Clinical Emergency County Hospital Craiova (period 1981-1993), which demonstrated that the number of patients considered in the Oncology County Cabinet is growing. In addition, demographic data provided by NSI was used, and thoroughness of the study was done by taking into account the distribution of the malignant neoplastic disease localization digestive priority in terms of: population structure and profile of Dolj county, area of residence, age groups predominantly affected and distribution new cases Craiova and the three subregions of Dolj County (North, South West and South East).

The study analyzed morbidity and mortality of malignant tumors of the digestive key locations and was looked at markers classics or incidence, prevalence and mortality.

CHAPTER VII. INTERPRETATION OF THE RESULTS

For a lot more suggestive representation in absolute render the composition recorded during the survey period, ie 2002-2012 and digestive cancers locations that were the subject of research (Table 4).

Table 4. Number of cases of digestive cancers depending on the location (absolute values).

<table>
<thead>
<tr>
<th>ESOPHAGUS</th>
<th>GASTRIC</th>
<th>COLON</th>
<th>RECTOSIGMOIDIAN JUNCTION</th>
<th>RECTUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>210</td>
<td>1322</td>
<td>1180</td>
<td>305</td>
<td>759</td>
</tr>
</tbody>
</table>
Neoplastic disease overall ranking for the period studied, 2002-2012, out on a priority locations digestive neoplastic disease, gastric cancer with 1322 new cases (35%), followed by colon cancer with 1,180 cases (colon 31%), both to large differences from the location of the esophagus (6%) and at the rectosigmoidian junction (8%). With a relatively high percentage and location is positioned in the rectum with 20% of all digestive localizations.

Of the 3776 cases recorded in the ten years that was done observational study, 209 cases (5.56%) are localized esophageal cancers. Of these, 83.25% are attributed to men, women are underrepresented (35 cases). Most cases belong to rural areas.

Gastric cancers represent 35% of all cases that were the subject of this study, 65.28% (863 cases) of the 1322 cases of localized cancers of the stomach are attributed to men. More than half of diagnosed cases (55%) are recorded in rural areas.

The highest number of localized colon cancer is attributed to men in a percentage of 53.72% of the 1,180 cases diagnosed in 2002-2012. Also distribution of cases for the two residence is in favor of urban areas (61.35%) found a big difference to the rural 269 cases respectively.

Rectosigmoidian junction location at the junction by the high percentage ie 59% cases is the preserve of males. With such a high percentage, 62%, where localized to the rectosigmoidian junction are assigned urban environment

Regarding the location of the rectum level, 472 men were diagnosed accounting for more than half of all cases (62.18%). The area of residence of the recorded cases of cancer of the rectum was urban areas with new cases 404 representing 53.22% of the total of 759 cases of rectal cancer.

Most deaths were recorded in the batch cancers represented by esophageal localized followed by gastric cancers, and colon and the fewest at the rectosigmoidian junction.

CHAPTER VII. CONCLUSIONS. PROPOSALS

The study "Linking environmental factors digestive cancers" allowed the following conclusions:

1. The incidence of localized digestive cancers as the most important indicator of morbidity increased in the period under review in the county of Dolj, and is growing steadily nationwide

2. Prevalence and mortality of these localizations of neoplastic disease follows the same increase as the incidence
3. Dolj County presented most new cases of digestive cancers in the period studied location from all counties in the region of South-West Oltenia.

4. The study prioritize the digestive localizations, the first location being gastric followed in order by: colon, rectum and anus (CCR), all at a significant distance from the location of the esophagus and the small intestine.

5. The incidence of gastrointestinal neoplasms is influenced by the age composition of the population and steadily increasing as the population ages.

6. For the city of Craiova was found that both locations have a maximum incidence, the highest values being recorded for colorectal neoplasm.

7. Risk and protective factors in the environment, specific and digestive cancers analyzed in this material are of major importance for understanding the current opportunities for identifying disease-risk groups of the population.

8. For better correlation between the risk factors involved as necessary strategies and coordinated efforts to promote health for the entire population of Dolj county.
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