COLORECTAL CANCER - EPIDEMIOLOGICAL PERSPECTIVES IN THE ONCOGENETIC CONTEXT

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COLORECTAL CANCER - EPIDEMIOLOGICAL PERSPECTIVES IN THE ONCOGENETIC CONTEXT (Abstract): The neoplastic pathology is one of the challenges of modern medicine, both in terms of epidemiology (morbidity, mortality and risk factors), as well as in terms of prevention, diagnosis or treatment. The progress of knowledge regarding risk factors and the identification of new diagnosis or therapy methods in the management of patients with colorectal cancer have led to a series of approach changes which create new perspectives not only for those affected by the disease, but also for their families. Risk factors for CRC include: modifiable factors (endogenous and exogenous factors) and non-modifiable factors (genetic factors). The risk of an individual belonging to the general population to develop CRC at a certain point in life is of 5%, while the risk of a subject with Lynch syndrome may reach 70-80%. The genes which potentially increase the risk of CRC include: MMR, MLH1, MSH2, MSH6 (high-penetrance genes) and APC, BRAF, CTNNB1 / beta-catenin, FBXW7, KRAS, PIK3CA, SRC and P53 (low-penetrance genes). The most used methods of screening for the general population are: the HEMOCOLL test, the colonoscopy and the flexible sigmoidoscopy, while for the groups at risk (with one or more risk factors) these include: the oncogenetic investigation (including the assessment of family history of familial adenomatous polyposis (or FAP), attenuated FAP (AFAP), hereditary non-polyposis CRC (HNPCC), personal history of colorectal cancer or adenoma, chronic ulcerative colitis and Crohn’s disease and molecular testing of individuals with risk factors). **Key words:** COLORECTAL CANCER, EPIDEMIOLOGY, INCIDENCE, SURVIVAL, RISK FACTORS.

Neoplastic pathology is one of the challenges of modern medicine, both in terms of epidemiology (morbidity, mortality and risk factors), and in terms of prevention, diagnosis or treatment. The estimated incidence per year has an upward trend from 10 million new cases in 2000 to 15 million in 2020 (1), cancer mortality being ranked 2\textsuperscript{nd} after cardiovascular diseases.

Colorectal cancer (CRC) is a real public health issue both in Romania and worldwide, which is accounted for by the mor-
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Bididity and mortality recorded. The evolution of progress regarding the knowledge related to risk factors and the identification of new diagnosis or therapy methods in the management of patients with colorectal cancer have led to a series of approach changes which create new perspectives not only for those affected by the disease, but also for their families (2, 3).

CRC is the third oncological pathology in the world in terms of incidence (with approximately 1-2 million new cases each year); it is the second pathology in terms of prevalence and the fourth cause of death in the world (with 600,000 deaths annually) (4). At a worldwide level, there is a wide variation in incidence, but the geographical pattern is similar for women and men. Colorectal neoplasia is the 3rd most common cancer type in men (10% of all cancers) and the 2nd most common cancer in women (9.2% of the total), 55% of cases being identified in more developed geographical areas. Regarding the global mortality rate, the variability is low, with the highest percentage recorded in Central and Eastern Europe (20.3 deaths / 100,000 men and 11.7 deaths / 100,000 women). Most deaths (52%) were recorded in less developed countries, where the survival rate is lower. In Romania, there is also an upward trend in the CRC incidence in both sexes – the male / female ratio is of 1/3 and is rapidly growing; for every 10 years of life after the age of 45 the numbers double (4).

**RISK FACTORS**

**CRC risk factors** include: age (over 40% of cases involve patients aged over 75); gender (more common in men); diet (high in red meat or processed meat and animal fats); obesity and overweight; alcohol consumption; smoking; occupational exposure to carcinogens (asbestos); ionizing radiation; presence of infection history; various medical conditions (adenomatous polyps, inflammatory bowel disease-Crohn’s disease, ulcerative hemorrhagic rectocolitis, biliary lithiasis, diabetes, metabolic syndrome); personal history of cancer (colorectal, oesophageal, laryngeal, lung, prostate, endometrial and breast cancer, as well as chronic lymphocytic leukaemia or melanoma); family history and genetic syndromes (familial adenomatous polyposis; hereditary nonpolyposis colorectal cancer; BRCA1 mutations) (5). Risk factors for cancer are multiple, presenting a low positive predictive value, except hereditary risk factors. Genetic predisposition for the development of malignancies due to genetic modifications is 70-80%, which is the only risk factor that reaches the positive predictive value, justifying medical and oncogenetic monitoring.

The risk of an individual belonging to the general population to develop CRC at a certain point in life is 1 out of 20 (5%), while the risk of a subject with Lynch syndrome may reach 70-80% (6).

**Hereditary CRCs** are classified into two main groups: polyposis forms, which include *Familial Adenomatous Polyposis* (FAP), *attenuated FAP* (a subtype of FAP in which the subject has less than 100 polyps and colorectal cancer that occurs at a young age), *Gardner syndrome* (a subtype of FAP which is accompanied by benign tumors of the skin, soft tissue and bones) and nonpolyposis forms, comprising: *Lynch syndrome* (LS) / hereditary nonpolyposis CRC (Hereditary Nonpoly-posis Colon Cancer) (HNPCC), *Turcot Syndrome* or *Peutz-Jeghers Syndrome* (7, 8).

The genes that modify the risk of CRC include: genes with major contribution
(high-penetrance genes): MMR, MLH1, MSH2, MSH6 and genes with variable contribution (low-penetrance genes), for which the most common somatic mutations of CRC described by Roy and Majumdar in 2012 appeared with genes such as APC, BRAF, CTNNB1 / beta-catenin, FBXW7, KRAS, PIK3CA, SRC and P53 (9). Genetic instability (10) in hereditary CRC is due to germinal mutations in the APC gene for cases diagnosed with FAP / attenuated FAP (9) and to DNA repair gene mutations (MMR) for cases of Lynch Syndrome (LS) (11, 12). This genetic instability in the case of FAP has its origins in the germ-line mutations of the APC gene on chromosome 5q21-22, but it may also exist in the MYH gene. Lynch syndrome is caused by mutations in DNA repair genes, namely MLH1, MSH2, MSH6, PMS2 (13). Among these, MLH1 and MSH2 genes, which cause a high level of instability, are responsible for the appearance of more than 90% of the cases of LS (14), in contrast to the 10% of cases attributed to mutations in the MSH6 gene, which causes a partial deficiency of MMR functions (13). The presence of hereditary mutations in MLH1 vs. MSH2 is associated with an increased risk of developing extra-colonic malignancies (15, 16).

SCREENING (EARLY DETECTION)

Screening methods for the early detection of colorectal cancer, evaluated by numerous studies, include tests for the detection of occult blood in the feces, colonoscopy, flexible sigmoidoscopy and double contrast triography. Recently, some modern and non-invasive methods have been introduced – virtual colonoscopy and genetic testing of feces for neoplastic DNA (17).

Currently, there are different types of faecal occult blood tests: Faecal Occult Blood Testing (FOBT), Hemoccult SENSA (a guaiac test, but more sensitive) Heme-Select (a test to detect human hemoglobin by immunochemical methods) or Hemo-Quant (for quantitative detection of faecal occult blood by means of fluorescent light) (18), but the most used is the Hemoccult test, which involves the detection of fecal occult blood by using an indicator substance (guaiac) impregnated on a piece of paper. The test is not specific to CRC, as there are also other non-cancerous lesions that may be tested by using this method. False positive results (about 2-6%) may occur in case of colorectal polyps, diverticulitis or anorectal lesions (hemorrhoids, fissures, rectitis). A big disadvantage of the Hemoccult test is represented by the false negative results (40% of cases), which may be due to: the presence of vitamin C in the diet, failure to follow a high-residue diet, use of expired tests, degradation of hemoglobin by bacteria in the colon or a cancerous lesion that is not bleeding when the faeces sample is collected. Other disadvantages include: the need to collect 3-6 faeces samples (due to the intermittent bleeding) and the high specificity only for the lesions of the left colon. In its non-hydrated form, the Hemoccult test has a sensitivity of 72-78% and specificity of 98%; after rehydration, the sensitivity of the test increases to 88-92%, but the specificity drops to 90-92% (17, 19). Another test used in the detection of feces occult blood is the Fecal Immune Test (FIT), which, although it has proved to be a more reliable screening method as it is based on a “Ag-Ab” reaction, does not replace the common use of the Hemoccult test because it is more expensive (20).

A modern approach to the early detection of CRC involves the use of DNA
markers, RNA and protein as diagnosis strategy (*Faecal DNA and RNA Test*). These molecular tests are non-invasive and are based on the fact that the neoplastic cells (CRC) have a high mitotic index and a low adhesion to the basal membrane, which facilitates their *continuous* exfoliation into the lumen of the colon (as opposed to the *intermittent* loss of blood detected by FOBT) used for molecular analysis (17).

*Colonoscopy* is considered a method of maximum accuracy for the diagnosis of CRC and of colorectal polyps (“golden standard”), which allows multiple and targeted biopsy of lesions detected in the lumen of the colon as well as polyp resection. The literature shows that colonoscopy can allow visualization of the caecum in 98.6% of cases. The sensitivity of the method is of 96.7% for the detection of cancerous lesions of and of 85% for the detection of large polyps, but it falls to 78.5% for the diagnosis of polyps sized <5 mm; its specificity is of 98% (21).

Following the results of numerous epidemiological studies which support the idea that the risk of developing colorectal cancer decreases when precancerous lesions are removed (adenomatous polyps), *flexible sigmoidoscopy (FS)* was recommended to be used as a screening method. Sigmoidoscopy has the advantage that, in comparison with colonoscopy, it requires less preparation time and is usually performed without sedation, but has the great disadvantage that it only detects distal colon cancers. *FS* (of 60 cm) has replaced rigid rectosigmoidoscopy because it can help to explore a larger segment of the colon and is better tolerated by patients. Compared to the *Hemoccult test*, FS has the advantage that it can help to directly visualize the colon or to identify and take targeted biopsy samples from the detected lesions (17).

Although *computed tomographic colonography* (CT colonography or CTC) or *virtual colonoscopy* is better accepted by the investigated subject compared to colonoscopy, in the case of symptomatic patients it is still little explored for screening (22). Sedation is not required for this technique, yet preparation is necessary in conventional colonoscopy. Meta-analysis studies reveal that sensitivity and specificity in CT colonography are high for identification of polyps > 10 mm (82%), but not for smaller polyps (56% for polyps ≤5 mm and 63% for lesions between 6 and 10 mm) (17). Although its use as a first option for CRC screening is unclear, the American Gastroenterological Association recommends CT colonography every five years (21).

**Other Exploratory Techniques.** There are many new endoscopic techniques (wide-angle colonoscopy, capsule endoscopy, narrow band imaging, auto-fluorescence imaging system, etc.) that are still in the evaluation stage but appear to be promising for CRC screening, as they will help to increase the CRC rate detection, especially for proximal colon and they will improve the population acceptability (17). The effectiveness of these methods will be evaluated after a period of time of use (23, 24).

The logical approach in the management of the case of hereditary CRC where a mutation of the genes involved in increasing the risk for cancer (MMR, APC) was identified, early detection of subjects at high risk of developing this neoplasia (*oncogenetic screening*) and adequate monitoring through personalized oncogenetic supervision of these subjects, of patients operated for colorectal cancer, and of their families represent a modern approach to be
included in current strategies for colorectal cancer prevention.

The consequence of detecting a mutation is the placement of the patient under oncological supervision and the application of primary, secondary or tertiary prevention measures such as: adaptation / modification of medical or surgical therapeutic measures, differentiated use of screening and early diagnosis measures (onset at younger age, high frequency, special tests) or individualized application of preventive measures: removal of polyps, etc. (25, 26). Subjects who present mutations in the APC gene are monitored regularly by repeating the colonoscopy every 2-3 years since adolescence. The frequency of testing is adjusted according to the number, size and character of the polyps. Besides monitoring, risk reduction strategies such as colectomy or procto-colectomy can be proposed given that the risk of cancer onset reaches 100% at the age of 50 and that the peak incidence of occurrence is during the 3rd decade of life (26).

CONCLUSIONS
A review of risk factors, of main early detection methods and of other methods of prevention for colorectal cancer reveals the evolution recorded in the management of patients with this pathology. The main risk factors include: age; gender (more common in men); diet (high in red meat or processed meat and animal fats); obesity and overweight; alcohol consumption; smoking; occupational exposure to carcinogens (asbestos); ionizing radiation; presence of infection history; various medical conditions (adenomatous polyps, inflammatory bowel disease – Crohn’s disease, ulcerative hemorrhagic rectocolitis, biliary lithiasis, diabetes, metabolic syndrome); personal history of cancer (colorectal, esophageal, laryngeal, lung, prostate, endometrial and breast cancer, as well as chronic lymphocytic leukemia or melanoma); family history and genetic syndromes (familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer; BRCA1 mutations). The most used methods of screening for the general population are: test HEMOCCULT, colonoscopy and flexible sigmoidoscopy, while the risk groups (with one or more risk factors) these include: the oncogenetic investigation (including the assessment of family history of familial adenomatous polyposis (or FAP), attenuated FAP (AFAP), hereditary nonpolyposis CRC (HNPCC), personal history of colorectal cancer or adenoma, chronic ulcerative colitis and Crohn’s disease and molecular testing of individuals with risk factors). Among the preventive measures, genetic screening in high-risk groups and individualized oncogenetic monitoring stand out as modern approaches. Oncogenetics will have an essential contribution in the early detection of hereditary risk cases as well as in the effective management of patients diagnosed with this condition, which, given the epidemiological evolution of the phenomenon, has proved to be one of the major public health issues at present and in the near future.

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**HORMONAL CONTRACEPTIVES, GENITAL TRACT INFECTIONS AND HIV RISK**

The hormonal contraceptives and genital tract infections are associated with altered cervical immunity. A recent study that evaluated changes in cervical immunity after taking hormonal contraceptives showed that the women who used injectable depot medroxyprogesterone acetate and those who use estrogen-progesterone oral contraceptives had increased levels of proteins that attract HIV host cells. Also, the effect of hormonal contraceptives was exacerbated in presence of disturbed vaginal microbiota or genital tract infections such as gonorrhea, chlamydia, genital herpes, trichomoniasis and candidiasis. The levels and the type of immune mediators, infection status and hormonal contraceptives increase HIV risk by their cumulative action (Fichorova RN, Chen P-L, Morrison CS, Doncel GF, Mendonca K, Kwok C, Chipato T, Salata R, Mauck C. 2015. The contribution of cervicovaginal infections to the immunomodulatory effects of hormonal contraception. mBio 6(5):e00221-15. doi:10.1128/mBio.00221-15).

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