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Colorectal cancer epidemiology and risk factors

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Abstract: *Colorectal cancer is an important health problem, being the third most frequent cancer pathology both in men and women. Programmes have been developed to decrease CRC incidence and mortality, including primary prevention strategies focusing on population education regarding diet and physical activity and secondary prevention programmes such as screening. Modifiable risk factors are known to be diet, obesity, smoking, alcohol and read meat consumption. Non-modifiable risk factors are age, inflammatory bowel disease, genetic syndromes and family history of colorectal cancer.*

Keywords: *colorectal cancer, risk factors, genetic syndromes, Lynch syndrome, diet, obesity, diabetes*

Colorectal cancer is an important cause for mortality and morbidity all over the globe and recent data from the United States of America report it as the third most frequent cancer pathology both for women and men. [1]

According to American Cancer Society, the risk for developing colorectal cancer during lifetime is 1:23 for men and 1:15 for women. [2] In industrialised western countries, the lifetime risk for such malignant pathology is approximately 5%. [3]

World Health Organization reports approximately 1.9 million new cases every year. [4] Incidence and morality due to colorectal cancer increase with age, most of the cases being diagnosed around 70 years of age. [5] During last years, it has been reported an increasing in incidence with 1 % for people 50 to 64 years of age and by 2 % for people younger than 50 years. [6] Because of increasing life expectancy, people migration and changes in daily habits, it is expected that by 2035, there will be 2.4 million new colorectal cancer cases world wide. [5]

In Romania, the incidence of CRC is 10.1/100000 in men and 7.3/100000 in women. [4]

All over the world, strategies have been developed in order to reduce colorectal cancer incidence and mortality. These strategies cover primary prevention such as educational programmes for healthy life style and secondary prevention, such as screening programmes. [7, 8]

Regarding the risk factors involved in colorectal cancer pathogenesis, they can be divided into two major groups:

1. Non-modifiable risk factors: age, sex, personal history of adenomas, personal history on inflammatory bowel disease, family history of colorectal cancer or genetic syndromes

2. Modifiable risk factors: diet, physical activity, weigh gain, medication, alcohol consumption and smoking

1. Age is an important non-modifiable risk factor, as colorectal cancer risk starts to increase after the age of 40, and most of cancers are diagnosed after 50 years, with a

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maximum of incidence between 60 and 70 years of age. [9] Latest reports show an increase in CRC incidence in 20-49 years of age persons and so it becomes one of 10 most frequent cancers for this group. [6, 10]

As for differences between sexes, it appears that colorectal cancer is more frequent in men that in women, regardless of the age group, with 4.4% risk precent in men and 4.1% in women. [11] There is an interesting discussion regarding the distribution of precursor lesions in men and women. In women, adenomas are more frequent in proximal colon while in men, adenomas have a distal grow pattern. [12] This information in useful in choosing the best method for screening both in men and in women. [13]

During lifetime, the risk of developing a tubular or villous colorectal adenoma is approximately 19%. [14] 95% of sporadic CRC develop from adenomas, as they are known to be precursor lesions. [15] Interestingly, not all adenomas evolve in colon cancer. Most of them will regress. It usually takes approximately 10 years for a polyp to transform in a malignant tumor. [16] So there is an opportunity window in order to discover precursor lesions through screening. This is why people with personal history of adenomas should be monitored with colonoscopy, in order to decrease the risk of developing colon cancer. [17] Also, an important topic to debate in this case is the role of modifiable risk factors that maybe influence in a positive manner by reversing the process of transformation from adenoma to carcinoma. If it is really so, it would be quite difficult to demonstrate it.

Another important risk factor for developing colorectal cancer is the personal history of inflammatory bowel disease, meaning Crohn disease and ulcerative colitis. The severity of endoscopic and histologic inflammation, the duration and the extent of colorectal lesions are important elements that increase the risks of neoplasia. [18, 19, 20] Patients with inflammatory bowel disease have a sixth time higher risk of developing colorectal cancer, comparing to normal population, and the risk is even higher for those with extensive colitis. [21]

Although approximately 75% - 80% of colorectal cancers are sporadic forms, the rest of 20-25% are diagnosed in persons with familial history of colorectal cancer [22] especially in first degree relatives of patients with colorectal cancer diagnosed before 60 years of age [23]. In these familial cases, genetic factors and life style work together.

Genetic syndromes are involved in 5-10% of diagnosed colorectal cancer. The best known and studied genetic syndromes are:

- Lynch syndrome - hereditary non-polyposis colon cancer (HNPCC)

- Familial adenomatous polyposis (FAP) with its subtypes: attenuated FAP (AFAP), Gardner syndrome and Turcot syndrome

- MUTYH - associated polyposis (MAP)

- Peutz-Jeghers syndrome (PJS)

Lynch syndromes is the most common inherited CRC syndromes as it accounts for approximately 2-4% of cases. [24] The risk of developing colorectal cancer during lifetime is about 70-80% and the median age at diagnosis is usually around 40 years of age. [25] This hereditary syndromes is causes by a mutation detected in the genes responsible for DNA repair (for example MLH1, MSH2 or MSH6). People with this condition can also develop gastric, pancreatic or uterine cancers. [26]

In the case of familial adenomatous polyposis (FAP), the risks of CRC cancer is given by the germinal mutation of APC gene from chromosome 5q21. [27] In this case, the patient is diagnosed with hundreds or even thousands of polyps in colon and rectum having a major risk of transformation in colon or rectal cancer before the age of 20 years. [28] This disease is diagnosed in less than 1% of population. [27]

People with AFAP are diagnosed with less than 100 polyps during colonoscopy and the higher risk of colorectal cancer is around the age of 40. [29] Regarding the other attenuated forms of FAP, the high risk for colorectal cancer remains and is associated with other forms of non-cancerous tumours of skin, bones or soft tissue as in Gardner syndrome or with medulloblastoma as in Turcot syndromes. [24, 28]

In MUTHY-associated polyposis, the risk of cancer is also reported at a young age. In this case, colon polyps appear because of MUTHY gene mutation, a gene that is involved in "proofreading" the DNA. People with this condition also have an increased risk of thyroid and other gastrointestinal cancers. [29]

Peutz-Jeghers syndrome appear because of STK11gene mutation. Is a very rare syndrome. It is associated with increased risk of hamartomas in digestive tract and breast, ovary and pancreatic cancer, beside colon cancer. [30]

2. Taking into consideration that 75-80% of colon cancer are sporadic forms, it is considered that environmental, dietary, cultural, educational and social factors play an important role in this disease occurrence and, by educational programmes, it is a preventable cancer. This statement is supported by population studies focused on health of migrants and their children. It was observed that in migrants that came from low incidence colorectal cancer countries,

the incidence of this neoplasia starts to increase during lifetime and their children have the same incidence of colorectal cancer as the people in the adoptive country [31, 32]. Also, the incidence is higher in urban area than in rural area. [32]

For many years, a large number of studies and meta-analysis tried to pinpoint the risk factors for colorectal cancer. The conclusion was that high consumption of read meat or processed meat, heavy alcohol consumption and smoking, high mass index and lack of physical activity are clear factor that can raise the risk ok colon cancer. [33-35] Data show that by consuming 5 portions of red meat per week, one can have a 13% increased risk of developing colon cancer. [28] In contrast with this data, fruit and vegetables can reduce the risk of colorectal cancer by 15% if consumed for as many as 3 portions per day. [36]

Alcohol and smoking are considered to produce inflammatory damage of normal colon mucosa, leading to formation of polyps. Although the exact mechanism by which alcohol affects colorectal mucosa is not completely understood, in the case of cigarette, it is considered that carcinogens are the ones to be incriminated in this process.[37] Studies showed that there is a 3 fold higher risk for smokers to develop colon polyps. [38]

Weight gain and maintaining a high body mass index can promote inflammatory state through inflammatory cytokines and adipokines. [39] This process favours angiogenesis and colon carcinogenesis. In this case, the protective role of NSAID, in reducing inflammation, especially Aspirin is quite easily to be understood. [40]

The EPIC study demonstrated that by adopting a healthy life style, meaning weight control, sustained physical activity, lack of smoking, low consumption of alcohol and read meat can actually decrease the risk of developing colorectal cancer. [41]

Given the important role of diet, constant exercise and maintaining a normal body index in preventing colorectal cancer and consistent with EPIC study results, World Cancer Research Fund/American Institute of Cancer Research (WCRF/AICR listed a number of recommendations for healthy population and also for colorectal cancer survivors [42] A summary of these recommendations is:

- Body mass index - one should maintain as thin as possible without becoming underweight

- Physical activity - at least 30 minutes per day

- Restrict as much as possible sugary drinks

- Consume vegetables and fruits

- Limit red meat and avoid processed one

- Limit alcohol intake

- Limit salt consumption

- It is preferred to have all nutrients mostly from diet and less from supplements

- Breastfeeding for women

An interesting discussion is linked to patients with diabetes. It appears that they have a higher risk of colon cancer, although this can be related to increased body mass and sedentary, studies demonstrated that even with correct diet and physical activity, they still have an increased risk of CRC than that of general population. [34]

Also, the use of insulin in the treatment of diabetes it appears to be related to a higher risk of CRC diagnosis and a worst prognosis than the patients with diabetes treated with metformin. [43]

Much discussion takes place in the last 10 years regarding microbiota role in colorectal cancer carcinogenesis. It is certain that in patients with colorectal cancer, colonic dysbiosis is reported. Several bacterial species might play a role in CRC such as Streptococcus bovis, Enterococcus faecalis, Fusobacterium spp or Bacteroides fragilis [44-46] Pro-carcinogenic results of the presence of these micro-organisms are described to be: genotoxicity, inflammation, oxidative stress, host defence regulation [47] More studies are in progress analysing the correlation between microbiota composition changes and molecular pathways of colorectal cancer

CONCLUSIONS

Taking into account all the modifiable risk factors, the need for primary prevention programmes is clear in order to decrease the burden of colorectal cancer incidence.World Health Organisation listed recommendations to be taken into consideration by general population regarding diet, physical activity and weight control.

Regarding non-modifiable risk factors, the secondary prevention programmes must be considered crucial for people with family history of colon cancer or for those diagnosed with inherited familial syndromes.

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