

## ONCOLOGICAL COUNSELING OF PATIENTS AND FAMILIES WITH HEREDITARY COLORECTAL CANCER

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### Summary

Colorectal cancer (CRC) is the third most common malignancy in the world. Thirty percent of all CRC cases are hereditary or familial forms of the disease. Approximately 5% of them represent well defined hereditary syndromes. Colon cancer syndromes are inherited autosomal dominant diseases, with exception of MUTYH associated polyposis, which is inherited in autosomal recessive manner. Most of CRC syndromes also carry significant risk of developing cancers of extra colonic localization. The clinician who deals with hereditary CRC patients should have a wide knowledge of presentation, genetics and cancer risks in hereditary CRC syndromes. In Croatia we do not have the center that systematically deals with CRC genetics, pharmacogenetics and hereditary CRC syndromes. Therefore, with this article, we systematically review the characteristics CRC syndromes.

KEYWORDS: *hereditary, colorectal cancer, familial adenomatous polyposis, Lynch syndrome*

### ONKOLOŠKO SAVJETOVANJE BOLESNIKA I OBITELJI OBOLJELIH OD NASLJEDNOG KARCINOMA DEBELOG CRIJEVA

#### Sažetak

Kolorektalni karcinom je treći najčešći maligni tumor u svijetu. 30% slučajeva su nasljedni i familijarni oblici bolesti. Približno 5% nasljednih oblika čine dobro definirani nasljedni sindromi kolorektalnog karcinoma. To su nasljedne autosomno dominantne bolesti, s izuzetkom tzv. MUTYH polipoze koja se nasljeđuje autosomno recesivno. Većina nasljednih sindroma kolorektalnog raka nosi rizik razvoja karcinoma drugih lokalizacija. Kliničar koji sudjeluje u liječenju oboljelih od kolorektalnog karcinoma trebao bi imati široko znanje o kliničkoj slici, genetici i rizicima za pojedine tumore u nasljednim sindromima kolorektalnog raka. U Hrvatskoj još uvijek nemamo centar koji bi se sustavno bavio genetikom kolorektalnog karcinoma, farmakogenetikom i nasljednim sindromima kolorektalnog raka. U ovom članku donosimo pregled i karakteristike nasljednih sindroma kolorektalnog raka.

KLJUČNE RIJEČI: *nasljedni, kolorektalni karcinom, familijarna adenomatozna polipoza, Lynchev sindrom*

### INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy. Different studies confirmed

that approximately 30% of all CRC cases are hereditary forms of the disease. Approximately 5% of them are associated with mutations of the genes that are highly penetrant and represent well de-

finer syndromes. Etiology of the remaining 20-30% is not well understood: cause being a mutation in a single genes that regulate metabolism or environmental factors or the interplay of both. In this article, we review the characteristics of well known CRC syndromes. Although some similarities do exist, they differ in clinical presentation, genetics and cancer risks. Identification of crucial genes improved the understanding of molecular mechanisms of CRC (1-3). The accumulation of genetic data required a clinician to interpret this data and out them into clinical context- their role in multidisciplinary colorectal cancer management is gaining weight.

### LYNCH SYNDROME

Lynch syndrome accounts for 2-4% of all hereditary CRC syndromes. Patients with Lynch syndrome are prone to various malignancies, predominantly colon and endometrial. Colon polyposis is possible but not common. The lifetime risk of developing CRC is 50-80%. Lesions in Lynch syndrome have more proximal location comparing to sporadic cases. They are also characterized by a high level of microsatellite instability (MSI), that is a feature of DNA mismatch repair (MMR) genes. Cancers with MSI have better prognosis than those without it.

Endometrial cancer is the most common malignancy outside the colon. Other include ovarian, gastric, ovarian, biliary small bowel, urinary tract, brain and pancreatic.

Lynch syndrome is the result of mutations in genes of DNA MMR that are important for genomic stability. These genes include hMSH2, hMLH1, hMSH6, and hPMS2. Of all Lynch syndrome cases, 90% are in hMSH2 and hMLH1 genes. Mutations in hMSH6 account for approximately 10%. Recently, mutations in the EpCAM

Table 1.

#### AMSTERDAM CRITERIA I

- At least three relatives with CRC; all of the following must be met:
- I. One affected individual is a first degree relative of the other two
  - II. At least two successive generations affected
  - III. At least one CRC diagnosed before the age of 50 years
  - IV. Familial adenomatous polyposis has been excluded

Table 2.

#### AMSTERDAM CRITERIA II

- At least three relatives with colorectal, endometrial, small bowel, ureter, or renal pelvis cancer; all of the following must be met:
- I. One affected individual is a first degree relative of the other two
  - II. At least two successive generations affected
  - III. At least one tumor diagnosed before the age of 50 years
  - IV. Familial adenomatous polyposis has been excluded

Table 3.

#### BETHESDA GUIDELINES

- Requires at least one of the following:
- I. CRC diagnosed in a patient who is less than 50 years of age
  - II. Presence of synchronous, metachronous CRC, or other Lynch Syndrome -associated tumors, regardless of age
  - III. CRC diagnosed in a patient who is less than 60 years of age with MSI-H histology
  - IV. CRC diagnosed in an individual and one or more first degree relatives with a Lynch Syndrome -associated tumor, with at least one of the cancers being diagnosed under age 50 years
  - IV. CRC diagnosed in an individual and two or more first or second degree relatives with Lynch Syndrome -associated tumors, regardless of age

(epithelial cell adhesion molecule) gene, also known as TACSTD1, were found in some families with Lynch syndrome. In these families malignancies were with early onset and with multiple tumors.

To diagnose Lynch syndrome it is important to take a detailed family history. Initially, Amsterdam criteria I (Table 1) were developed to detect families that could have Lynch syndrome, but 50% of them failed to meet mentioned criteria. Improvement was made with Amsterdam II (Table 2) and Bethesda guidelines (Table 3). Families that fit these criteria require further evaluation. Genetic testing typically starts with analysis of hMLH1 and hMSH2 genes, because they account for the majority of cases. This is the first approach that includes high costs and low sensitivity. The second, cost-effective approach is to perform testing when any of the Bethesda guidelines are fulfilled. It begins with MSI and immunohistochemistry (IHC) analysis. Testing with IHC uses antibodies specific for hMLH1, hMSH2, hMSH6 and hPMS2 proteins to evaluate tumors for MMR deficiency. It can direct genetic testing to the mutated MMR gene.

Some models have recently been made to make a diagnosis of Lynch syndrome easier. They analyze the family history to estimate the probability that affected person carries MMR gene mutation.

The fourth approach to diagnosis is to test all CRC and endometrial cancers to MMR deficiency and it has discovered that Bethesda guidelines still miss 28% of Lynch syndrome.

It is important to identify individuals with Lynch syndrome because surveillance decreases the incidence of tumors and related deaths. Regular colonoscopy should be performed at 1-2 year interval, starting by age 20-25 years. When cancer appears, subtotal colectomy with ileorectal anastomosis is advised and annual surveillance thereafter.

Prophylactic hysterectomy and bilateral salpingo-oophorectomy is an option with women after completion of childbearing. Annual screening for these tumors is recommended after the age of 30 and prophylactic surgery after the age of 40 (1-5).

## FAMILIAL ADENOMATOUS POLYPOSIS

Familial adenomatous polyposis is the second most common CRC syndrome with the characteristic of developing numerous colon adenomas starting in early adolescence. If untreated, CRC is inevitable. 95% of patients with FAP develop CRC by the age of 50. Attenuated FAP is a less severe form of the disease with an average of 30 polyps, predominantly in proximal colon and a later age of CRC development. Gardner syndrome (FAP with epidermoid cysts, osteomas, dental anomalies, and/or desmoid tumors), FAP and attenuated FAP are a result of APC gene mutations.

As an extra colonic feature of FAP upper gastrointestinal tract polyposis can occur. The lifetime risk of developing gastric cancer is 1% and of duodenal cancer 4-12%. Extra colonic features are less common in attenuated FAP.

If more than 100 colonic adenomas are identified, a diagnosis of FAP can be made. Younger people can have fewer polyps and might also have FAP. If more than 10 but less than 100 polyps are found in a person older than 40 to 50 years, a diagnosis of attenuated FAP can be made. FAP and attenuated FAP are caused by alterations in APC gene that is tumor suppressor gene. In 25% of FAP *de novo* mutations can be found.

Patients at risk for FAP or if a diagnosis of FAP is already established should have regular colonoscopy every 1-2 years starting at the age of 10-12 years. Colectomy is performed when more than 20 adenomas develop, when they are more than 1 cm large or with malignant histology. If adenomas are present in the anorectal region, mucosal stripping is done. If rectum is preserved, annual endoscopic surveillance is necessary.

Individuals with attenuated FAP should have colonoscopy done every 1-2 years, starting before the age of 20 years. Regular 1-3 years period upper GI tract endoscopy should be done in patients with FAP or attenuated FAP at the beginning of 25-30 years. Patients with FAP also have an increased risk for thyroid cancer (1,6).

## MUTYH-ASSOCIATED POLYPOSIS

This syndrome is characterized by adenomatous polyps of colorectal region and higher risk of CRC. Polyposis occurs at the age of 40. It is caused by mutations in MUTYH gene which product is involved in defending against oxidative damage of DNA. The diagnosis is made by genetic testing for specific MUTYH gene variants. Patients with this syndrome often have proximal colonic lesions and surveillance is started at the middle 20s. The risk for upper GI tract tumors is similar to that in FAP (1,3).

## PEUTZ-JEGHERS SYNDROME (PJS) AND JUVENILE POLYPOSIS SYNDROME (JPS)

These syndromes are characterized with hamartomatous polyps and increased risk for CRC. People with PJS can be recognized by mucocutaneous pigmentations, typically present on the lips or buccal mucosa. These findings are absent in patients with JPS. The risk of developing breast and pancreatic cancer is also increased. Mucocutaneous telangiectasias, GI arteriovenous malformations and pulmonary arterio-venous malformations can occur in 15% of patients with JPS. PJS is caused by mutations in STK11 gene, whereas JPS is caused by mutations in either SMAD4 or BMPR1A gene. Colonoscopy every 2-3 years is advised, beginning with symptoms or in late teens if no symptoms occur earlier (1,5).

## HYPERPLASTIC POLYPOSIS (HPP)

Its feature are multiple large hyperplastic polyps of the colon with unknown etiology. It has also increased risk of CRC, usually at the age of 50 to 60 years. Lesions occur in the proximal colon. Rare familial cases of HPP have been reported. Regular colonoscopy every 1-2 years should be performed (1).

## FAMILIAL COLORECTAL CANCER

30% of all CRC examples are inherited. Patients' history and population studies revealed some less penetrant but more common susceptibility genes. These cases are defined only by family history. CRC risk associated with the common polymorphisms is affected by gene–gene and gene–environmental interactions. People who have a first-degree relative with CRC diagnosed over age 50 years have a 2–3-fold increased risk for this malignancy. In these cases, screening and surveillance are based on family history.

According to Jasperson et al. screening recommendations based on family history are as follows: 1) patients with a single first-degree relative over the age of 60 years with colon cancer should receive standard, average-risk colon cancer screening, but starting at age 40 years; 2) patients who have 1 relative with CRC under 60 years or 2 first-degree relatives with CRC should be screened every 5 years by colonoscopy, starting at age 40 years, or at an age 10 years younger than the earliest case in the family; and 3) patients with only second- or third-degree relatives with CRC should receive average-risk screening. There are more than 170 low penetrance genetic variations that can confer susceptibility to CRC. These loci were discovered by single nucleotide polymorphism (SNP) markers and account for only 6% of CRC cases. Individual's SNP profile can predict the risk of CRC and can be valuable to establish proper preventive measures (1,7-10).

## ENVIRONMENTAL FACTORS

Environmental factors that are speculated to influence CRC risk in predisposed individuals. In fact aspirin, NSAIDs, selenium, calcium and folic acid were related to CRC risk, however the results

of these studies are still debated. Recently, Zgaga et al. suggested causal relationship between 25-hydroxyvitamin D and CRC. There are also different alleles of CYP24A1 and CYP24B1 that affect colon cancer risk depending on vitamin D and calcium intake, ultraviolet exposure, gender and estrogen replacement therapy. Nevertheless, further studies are needed to identify optimal strategy for CRC prevention by pharmacological intervention or dietary intake recommendation (11-13).

## Genetic counseling

Genetic counseling is essential for interpreting results of oncological genetic testing and giving their context. Across European Union, it has been performed by both nurses and the physicians. The formation in genetic counseling EU varies from courses to subspecialty after specialty in pediatrics of clinical medicine. Ideally, interpretation of the results and counseling should be at the same location, available at institution which specializes in cancer care (Fig. 1.).

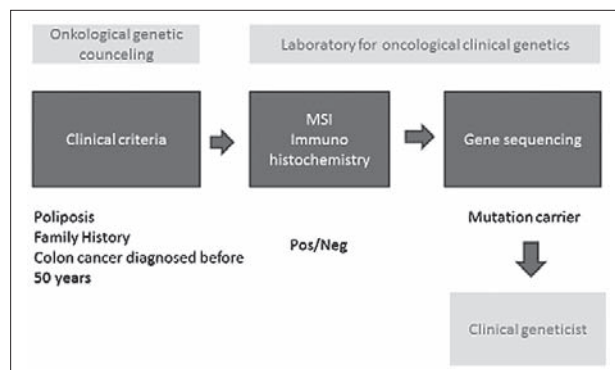


Figure 1.

## CONCLUSION

Colon cancer syndromes are inherited autosomal dominant diseases, with exception of MAP, which is inherited in autosomal recessive manner, and HPP, etiology is still not well understood. Analyses of CRC risk should be implemented in clinical practice; the most important step is detailed family history taking and analysis. Individuals with higher risk for CRC should get proper genetic counseling with adequate plan for future screening. Most of well defined CRC syndromes carry significant risk of developing cancer of extra

colonic location and the screening plan should take it into account. The clinician who takes care of CRC patient should have a wide knowledge of presentation, genetics and cancer risks in hereditary CRC syndromes.

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