RISK FACTORS IN COLORECTAL CANCER-LITERATURE REVIEW. WHY TO KNOW THEM?

Alexandra-Alina Vesa[1], Octavian Maghiar[2], Laura Maghiar[3], Ovidiu Pop[1], Andreea Diana Mudura[4], Adrian Marius Maghiar[2,5]

[1]University of Oradea, Faculty of Medicine and Pharmacy Oradea, Morphological Sciences Department - [2]University of Oradea, Faculty of Medicine and Pharmacy Oradea, Surgical Sciences Department - [3]University of Oradea, Faculty of Medicine and Pharmacy Oradea, Preclinical Sciences - [4]University of Maastricht, Health Professions Education-PhD Student - [5]Pelican Hospital Oradea, Chief of General Surgery Department

[*]*all authors have equal implication in this study*

ABSTRACT

Introduction*: Colorectal cancer (CRC) has recently seen a worrying rise worldwide. According to the latest data provided by GLOBOCAN 2020, the prevalence for the next 3 to 5 years show at least a doubling of cases worldwide. What is the cause of this growing incidence of this pathology? Studies have shown over the years that malignancies located at this level are multifactorial and a number of risk factors are implicated in their pathogenesis, recently paying more and more attention to the genetic involvement.*

Materials and methods*: Our main goal for this article was to recapitulate these colorectal cancer risk factors, using the latest and previously provided data, thus obtaining as new and accurate information as possible. We have focused more on genetic risk factors, which are increasingly being mentioned and identified in various cases diagnosed with colorectal cancer.*

Results*: We have managed to gather the latest data on the mutational status in this oncological pathology, since the molecular and genetic studies are gaining more and more ground in medical practice.*

Conclusion*: Why bother in trying to identify these factors? Given the explosion of new cases of colorectal cancer, identifying these risk factors can be of huge benefit to the recognition and inclusion of people in the high risk category for the same purpose, namely that to prevent is better than to treat.*

Keywords: *colorectal cancer, risk factors, mutational status.*

DOI: 10.19193/0393-6384_2022_5_474

Received *January 15, 2022;* ***Accepted*** *June 20, 2022*

Introduction

It seems that genetic factors together with environmental factors play a very important role in the pathogenesis of colorectal cancer (CRC)[(1)]. Overall, most of the malignant tumors located in the colon and rectum (about 95%) are considered to be sporadic, which means that the genetic changes develop by chance after a person is born, therefore there is no risk of passing these mutational changes to the one's descendant[(2)]. Numerous risk factors have been incriminated in the evolution of colorectal cancer. Several studies have shown that those who have had cancer previously or a relationship with colon and/or rectal polyps, Crohn's disease, ulcerative colitis, diabetes mellitus, or procedures that resulted in the removal of the gall bladder, have an elevated risk of CRC. Aetiology of CRC is also influenced by lifestyle variables. Obesity, sedentary behavior, cigarette smoking, alcohol consumption, and a poor diet (low in fiber, fruits, vegetables, calcium, and high in red and processed meat) have all been associated to an elevated risk of CRC in recent studies. Colorectal cancer risk is also influenced by gut microbiota, age, gender, race, and socioeconomic status[(3)].

Age

In the United States, persons over 65 years old have a three times higher risk and are more likely to be diagnosed with CRC than the ones in between 50-64 years old, and about 30 times higher than those between 25-49 years old. The possibility of developing malignant tumours at this level rises as persons get older[4].

Colorectal cancer can as well develop in young adults and even in teenagers, but the majority of these cancers develop in persons past over than 50 years old. For malignant tumours located in the colon, the mean age at the time of diagnosis for men is 68 and for women is 72. For rectal cancer, mean age of diagnosis is 63 for both sexes[5]. Colon cancer may present as sporadic (approximate 70%), familial clustering (approximate 20%) and inherited syndromes (approximate 10%). For sporadic colon cancer, the average age of diagnosis is older than 50 years and is principally linked to environmental factors. This is not the case for a small percentage of patients who have a true inherited pattern that puts them at a higher risk at a younger age (less than 50 years).The remaining 20% are familial clustering in the complete absence of a recognizable inherited syndrome[6].

Fanny ER Vuik et al (2019) demonstrated an increase incidence, in adults aged 20-49 years in Europe. The largest increase in CRC incidence was seen among subjects aged 20-39 years. The incidence of colon cancer increased with 6.4%-9.3% / year and that of rectal cancer with 1.6%-3.5% / year[7].

In Canadian respondents aged 20–29 years, the incidence of colon cancer increased faster than the incidence of rectal cancer (6.2%, respectively 1.5%). Incidence for this type of malignant tumours, also rises in Australia and China, especially in the young adults category[8].

Gender

General incidence is higher in men, with an earlier age distribution. Even so, significant and important differences between the sexes depend also on the primary site where the tumour is located (anatomical location)[9].

An analysis of colorectal cancer incidence by the primary anatomical location of the tumour, shows that the proportions of malignant tumours in the rectum and sigmoid colon are higher in men (31.5% and 23.1%) than women (23.1% and 20.4%). In contrast, the proportion of cases with a tumour located in the caecum and ascending colon are higher in women (17.2% and 9.8%) than men (12.2% and 7.3%) and these tumours are usually harder to detect and diagnose, due to late symptoms[10].

Race, ethnicity

Several variables have been cited as contributing to the racial disparities[11]. Indeed, despite the significant declines in incidence and mortality among African Americans, CRC incidence and mortality remain greater among this group than among other racial and ethnic groups[12]. When compared to their white American counterparts, young African Americans (under 50 years) have a higher mortality rate. Moreover, studies showed an increased mortality risk in only African American men compared to Caucasians, with no differences among women[13].

CRC is the second most prevalent cancer diagnosed in Hispanic men and women[14]. African Americans (both sexes) and Japanese American women have a higher risk of colon cancer, while Japanese Americans (both men and women) and Native Hawaiian men have a higher risk of rectum cancer, according to site-specific studies[15].

Family history of colorectal cancer

A positive family history of colorectal cancer is a notable risk factor for CRC, as it encompasses both hereditary and environmental risk[16]. The lifetime risk of developing CRC for a person with only one affected first degree relative is almost twice that of persons that don't have any affected family member. Needless to say that the risk is even higher with more affected relatives and from here the younger age of CRC diagnoses in the family[17]. Personal or family history of CRC, previous existence of adenomatous polyps and/or villous or tubulo-villous polyps with dysplasia indicate a high risk for synchronous and metachronous CRC primary cancer up to 3% to 5% at 5 years or even longer after polyp resection, thus requiring a closer period of time for screening[18].

In a study performed by Nora B. Henrikson et al, the relative risk of developing CRC ranged from 0.89 (for persons without a positive family history) to just-about a 20-fold risk (for persons with likely inherited syndromes), with increasing family history burden. If the relative was diagnosed at an earlier age then the risk for CRC becomes even higher[16].

Rare inherited conditions

Only 5% of colorectal cancers develop in the setting of a well-established Mendelian inherited

conditions. Moreover, serrated polyposis is a clinically defined syndrome with development of numerous serrated polyps in the large intestine and rectum that has an increased risk for development of CRC. This disorders can be classified into two large groups -Hereditary non-polyposis CRC and Hereditary polyposis CRC)[19].

A.Hereditary non-polyposis colorectal cancer (HNPCC) represent an autosomal dominant cancer syndrome. The incidence of this syndrome is 1.7 to 4.2% among all CRCs patients, (3 to 8 cases / 1.000.000, according to GLOBOCAN 2018)[20].

1. Lynch syndrome is the most often seen from all hereditary cancers and corresponds with an increased risk of colorectal, endometrium, ovary, stomach, and small bowel cancer. Lynch syndrome has associations with mutations of DNA mismatch repair (MMR) as MLH1 (76%), MSH2 (40%), MSH6, PMS2, and EpCAM. (3 to 5 cases /1.000.000, according to GLOBOCAN 2018)[21,22].

2. Colorectal carcinoma-sporadic type, MLH1-/PMS2-deficient[23].

3. Muir-Torre Syndrome is due to mutations in DNA mismatch repair genes which eventually results in microsatellite instability. The distinctive features are sebaceous neoplasms of the skin and visceral malignancies with colonic carcinoma being the most usual[24]. (2 cases / 10.000.000, according to GLOBOCAN 2018)[25].

4. Turcot syndrome type I: The prevalence is approximately 20-25% among all Turcot syndrome. It is related to mutations of the mismatch repair gene[26].

B. Hereditary polyposis colorectal cancer (HPCC) accounts for approximately 3 to 5 % of all CRC cases. (5 to 9 cases / 1.000.000, according to GLOBOCAN 2018)[27].

1. Familial adenomatous polyposis (FAP) is an autosomal dominant polyposis syndrome. If it is left untreated, patients will develop hundreds (even thousands) of polyps throughout the colon and rectum. Polyps often develop in the early teens and result in a nearly 100% lifetime risk of colorectal cancer by 40 years old if untreated[28]. (2 to 3 cases / 1.000.000, according to the data from the Danish Polyposis Registry 2017)[29].

2. Adenomatous polyposis syndromes, like APC and MUTYH[30]. There is accumulating support suggesting that both loss of tumour suppressive function and gain of function of APC mutants play critical roles in the development of CRC[31].

3. Peutz-Jeghers syndrome: (STK11/LKB1: 1.2 / 1.000.000 inhabitants)[32].

4. PTEN hamartoma tumor syndrome: (PHTS; PTEN)[33].

5. Cowden syndrome is characterized by multiple benign hamartomas that can develop in any organ. Incidence of Cowden syndrome is 6 cases / 10.000.000[34].

6. Turcot syndrome type II: this type accounts for approximately 75- 80% among all Turcot syndromes. It is highly connected with the APC gene mutation([35].

7. Gardner syndrome is characterized by the presence of multiple adenomatous polyps that line the intestinal mucosa with a high potential for malignant transformation[36].

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD)-related colorectal cancer is accountable for about 2% of the annual mortality rate due to CRC overall, yet it accounts for 10–15% of the annual deaths in IBD patients. Patients with IBD-related CRC are diagnosed at a younger age than those with sporadic tumours, and their 5-year survival rate is roughly 50%[37]. Patients with persistent ulcerative colitis and Crohn's disease have a higher risk of developing CRC compared to the general population[38]. IBD and CRC have a similar prevalence worldwide, according to population-based studies, with an increased incidence in northern Europe and the United States. In addition, both UC and CD are associated with westernized habits[39].

Ulcerative colitis, an unrestrained colorectal process of inflammation, associated with systemic immune deregulation and impaired tumour surveillance, could play a part in the development of malignant tumours at this level. UC-associated CRC arose from a larger area of colorectal mucosa that was already suffering with a mutational burden that conferred eventually an increased tendency for further processes of dysplasia. This approach involved a separate sequence of genomic changes: inflammation → dysplasia → carcinoma[40,41].

Chronic inflammation in the intestinal mucosa destroys epithelial cells, leading to increased cell replication and/or direct DNA damage, which is now recognized as a risk factor for the development of CRC in UC/CD patients[42,43].

Smoking

Tobacco use appears to be a modest risk factor for the development of malignant rectal and colon tumours. Colorectal carcinoma is a heterogeneous group of neoplasms with numerous combinations of molecular alterations and complex interactions with host cells in the tumour microenvironment[44,45]. Evidence suggested not only the ability to induce cancer due to cigarette smoking, but also the immunosuppressive consequence of this toxic practice[46].

The cigarette smoke contains a hazardous cocktail of more than 7,000 toxic chemicals, including at least 70 known carcinogens that have the potential to harm nearly every system in the human body. These carcinogens may eventually reach the colorectal mucosa through direct ingestion or through the bloodstream and may have a direct neoplastic effect on both the colon and the rectum[47].

Smoking suppresses the function of cells associated with innate immunity (dendritic cells, NK cells, and macrophages) by that suppressing Th1 cell activity and inhibiting the immuno-surveillance processes[48]. Nicotine, which is the major component found in the cigarette smoke, acts as an agonist of nicotinic acetylcholine receptors and might specifically contribute to the suppression of the immune system. Nicotine not only that it activates signaling pathways like the RAS-RAF-MAP2K (MEK)-MAPK1 (ERK) pathway and JAK2-STAT3 pathway, but it also compromises anti-tumour monitoring process of the immune system along with suppression of NK cells and dendritic cells[49, 50].

Evidence indicates that smoking can increase the risk of MSI-high colorectal cancer, which is characterized by a powerful immune response to the tumour[56]. Cigarette smoking, both past and present, was linked to an increased risk of CRC, especially with MSI-high, BRAF-mutation, KRAS-wild-type and CIMP-high CRC[51].

Alcohol consumption

Alcohol consumption, a habitual and rising practice of modern society, represents one of the major risk factors for development of CRC. Epidemiologic studies suggest that even moderate drinking increases oncogenic risk. Metabolism of alcohol requires ethanol conversion to its metabolites, and that process might exert a carcinogenic consequence in the large intestine. The production of acetaldehyde and alcohol's other metabolites conducts to activation of cancer promoting cascades, like DNA-adduct formation, oxidative stress and lipid peroxidation, epigenetic alterations, epithelial barrier dysfunction, and immune modulatory effects. It is well-known that alcoholics themselves are predisposed to a poor unhealthy diet, low in folates and fibers, plus the disturbance of the circadian rhythm, which could further augment alcohol-induced colon carcinogenesis[52].

Alcohol's consumption and metabolism can lead to multiple molecular effects that can set in motion development of atypical cells[53]. Its oxidative and non-oxidative metabolism, and formation of by-products, such as reactive oxygen species and metabolites, can lead to an array of genetic, cell signaling, and immune processes. Reciprocity of all of these various processes can trigger the cancer pathogenesis cascade like cell proliferation, angiogenesis, modified and altered immune response, oncogenic expression[54,55,56,57].

Increases in alcohol use of 10 grams per day (10 grams of ethanol - 100 milliliters of wine, 275 milliliters of beer, or 30 milliliters of spirits) were linked to an increased risk of colorectal cancer. Results from a meta-analysis done by Cheng Zhang and Min Zhong found that beer drinkers were associated with almost 20 % increased chance of CRC, compared with persons that don't consume alcohol at all or with occasional alcohol drinkers. The risk was stronger in favour of rectal cancer that for colon cancer[59].

Diet. Physical activity

Undoubtedly, the latest studies suggest that CRC is an obesity-related cancer. Epidemiological analyses support a dose–response relationship between increasing excess body weight and CRC risk and the relationship holds for biomarkers of visceral fatness[60,61]. Leila Abar et al. found a link between all of the included anthropometric parameters (weight, BMI, waist circumference, and waist-to-hip ratio) and the risk of colorectal cancer, including all anatomical localizations (colon, proximal colon, distal colon, and rectum). The strongest association for BMI was noticed with location of malignant tumours in the distal colon, showing an 8% increased risk for every increase of 5 kg/m^2 of BMI. Increased risk of colorectal cancer due to increased BMI was seen more often in men than in women[62].

In a large population-based study performed by Prudence R Car et al (2020), similar certain associations were noticed in women and men

between higher BMI and risk of colorectal cancer. In correlation with the molecular changes of the tumour, higher BMI was distinctively associated with MSI, CIMP, BRAF, and KRAS CRC, in women, but without any meaningful differences in men. Furthermore, in women only, higher BMI was more strongly associated with increased CRC risk with tumour development mostly observed in the proximal colon or arising through the serrated pathway (tumour cell proliferation characterized by a combination of MSI-high or MSS, CIMP-high, and BRAF mutation). Also the study found consistently strong connections between BMI and risk of colon cancer (both proximal and distal colon) and rectal cancer in both men and women and provides further evidence that excess body fatness is an important potentially preventable cause of CRC[63]. Chronic inflammation has been reported for a long period of time to bestow to the development and advancement of many types of cancer, including also CRC. Pro-inflammatory dietary constituents generally include carbohydrates, proteins, total fat, trans fat, cholesterol, and saturated fatty acids. Fibers, polyunsaturated fatty acids, minerals, vitamins, anthocyanidins, isoflavones, and beta-carotene are all found in anti-inflammatory diets[64]. A "healthy" diet (more fruits, vegetables, whole grains, nuts, fish and other seafood, milk and other dairy products) was correlated with a reduced risk of colorectal cancer. In contrast, "unhealthy" diet (increase intakes of red meat, processed meat, sugar-sweetened beverages, refined grains, desserts) was correlated with a higher CRC risk[65]. Yogurt consumption has been shown to diminish the risk of colorectal adenomatous polyps with increased malignant potential[66]. Besides, gut microbiota dysbiosis also has a strong consequence on disease progress, and modifications in the intestinal microflora plus a decreased production of short chain fatty acids (SCFAs) seem to be a relevant risk factors. According to a study conducted by Gomes et al., increasing the level of SCFAs by influencing the colon microflora has the potential to prevent or even treat CRC[67]. White vegetables and fruits contain various phytochemicals and nutrients, such as the polysaccharides of apples, the glucans of mushroom, saponins of root and bulb vegetables, and the quercetin of onions and apples, which play important antioxidant roles and limit the DNA damage[68].

Genetic factors

CRC is a molecularly and pathologically heterogeneous disease. Different CRC subtypes can be distinguished based on the genetic alterations (KRAS or BRAF mutational status), or based on the site of the primary location of CRC (originating in the right or left side). These traits could be used to develop prognostic and predictive biomarkers for this type of cancer, which could be very beneficial in identifying and treating CRC[69].

Molecular changes that happen in colorectal cancer can be grouped into three main categories: Chromosomal Instability (CIN), Microsatellite Instability (MSI) and CpG Island Methylator phenotype (CIMP).

Microsatellites, also known as Short Tandem Repeats (STRs), are short (1-6 base pair) repeating DNA segments found throughout the genome. and approximately 3% of the human genome is made up of them. Microsatellites are prone to high mutation rank because to their persistent repeating structure. A significantly defective DNA mismatch repair (MMR) process causes microsatellite instability (MSI), a unique molecular change and hyper-mutable phenotype. It is defined as the existence of alternate-sized repeating DNA sequences that are not ordinarily present in the homologous DNA sequence. MSI is seen in the majority of malignancies, including sporadic colon and stomach cancer, sporadic endometrial cancer. Approximately 20% of colorectal cancers display MSI. Analysis of MSI status in CRC has prognostic and therapeutic implications, as well as diagnostic and can help even in the classification of the tumour. For these reasons, determining MSI in patients with colorectal cancer is becoming increasingly crucial[70]. Within these types, impacted pathways such as WNT, MAPK/PI3K, TGF-, TP53, and mutations in different genes such as c-MYC, BRAF, PIK3CA, PTEN, SMAD2 and SMAD4 and lastly RAS have been documented to be implicated in cell proliferation and surviva[71].

Despite the fact that the majority of CRCs follow a well-defined chromosomal instability pattern, approximately 12-15% have deficient DNA mismatch repair (dMMR) which is when the tumour has this hallmark of microsatellite instability. Tumours with the dMMR/MSI are caused by a mutation in one of the MMR genes (MLH1, MSH2, MSH6, PMS2), or, more commonly, epigenetic inactivation of the MLH1 MMR gene. CRCs with dMMR/MSI status have a definite phenotype that includes preference for the proximal area of the colon, poorly differentiated tumours (G3-histological grade), and profuse tumour infiltrating lymphocytes. These

tumours have a superior stage-adjusted survival than competent MMR or microsatellite stable (MSS) tumours, according to data from multiple studies, and they respond differently to 5-fluorouracil-based adjuvant treatment[72].

The human RAS genes (KRAS, NRAS and HRAS) are the most often mutated oncogenes in human cancer appearing in 90% of pancreatic cancers, 35% of lung cancers and in 45% of colon cancers. Because of these extreme circumstances, the RAS genes are one of the most important drug research targets in cancer. KRAS is the most commonly mutant isoform in pancreatic, lung, and colon cancer, while NRAS is the most commonly mutated isoform in melanomas and acute myelogenous leukemia, and HRAS is the most commonly mutated isoform in the urinary bladder[73]. Although KRAS gene mutations occur early in roughly half of all CRC cases, they are unlikely to be the key in the initiating events (loss of APC or mutations in beta-catenin in mismatch repair defective tumours). The extent to which these malignant tumours are dependent on KRAS mutation is still being investigated, but RAS is one of the most important therapeutic targets for cancer, even in CRC[74]. The MAPK pathway is the most basic and reliable KRAS-regulated signaling mechanism. When KRAS is activated either conventionally through receptor activation or through oncogenic mutations, KRAS proteins dimerise. The dimers subsequently attach to RAF kinases and activate them. Next, RAF can phosphorylate the two catalytic serine residues of MEK. MEK, a dual threonine and tyrosine recognition kinase, then phosphorylates other kinases in the pathway, namely ERK1 and ERK2. Activated ERKs trigger various effector pathways in healthy cells, including the G1/S phase transition, apoptosis inhibition and cell motility. KRAS mutations, in particular, have been shown to increase MAPK activity abnormally in CRC cells[75,76].

The status of KRAS mutations appears to influence the pattern of secondary tumour spread in CRC. Studies show a difference in the frequency of KRAS mutations in patients with liver, lung and brain metastases[77]. According to several research studies, metastatic CRC with a KRAS mutation is more likely to spread to the lungs than CRC with a wild-type KRAS mutation.(78) KRAS mutations cause tumour cells to proliferate uncontrollably, and when combined with other genetic alterations like the APC gene, they enhance tumour growth and progression[79].

Another finding was that right-sided CRC has a worse prognosis than left-sided tumours, and KRAS and BRAF mutations have recently been identified as cancer indicators with a negative prognosis[80].

Conclusions

Colorectal cancer is an oncological pathology that, unfortunately, has gained momentum in terms of incidence in recent years. The growing incidence of colorectal cancer is one of the most frequently addressed medical topics worldwide. Information presented in this paper shows the latest information about the risk factors of colorectal cancer and it is good to be up to date with the latest news considering that the figures for the next 3 years, according to GLOBOCAN 2020, show at least doubling of new cases diagnosed with colorectal cancer. The ability to identify these factors plus a correct and careful patient history can help prevent late-onset disease and implement more rigorous screening programs in the high-risk group.

References

1) Ernst J. Kuipers, William M. Grady, David Lieberman et al:COLORECTAL CANCER, Nat Rev Dis Primers. 2015; 1: 15065. Published online 2015 Nov 5. doi: 10.1038/nrdp.2015.65
2) Colorectal Cancer: Risk Factors and Prevention, https://www.cancer.net/cancer-types/colorectal-cancer/risk-factors-and-prevention, Approved by the Cancer.Net Editorial Board, 01/2021, last accessed 10.09.2021
3) Tomasz Sawicki , Monika Ruszkowska , Anna Danielewicz- A Review of Colorectal Cancer in Terms of Epidemiology, Risk Factors, Development, Symptoms and Diagnosis, Published: 22 April 2021
4) SEER*Explorer: An interactive website for SEER cancer statistics (Internet) Surveillance Research Program, National Cancer Institute; Available from https://seer.cancer.gov/explorer/. Accessed September 10 2021.
5) https://www.cancer.net/cancer-types/colorectal-cancer/risk-factors-and-prevention, last accessed 08.08.2021, Approved by the Cancer.Net Editorial Board, 01/2021
6) Allen J, Sears CL. Impact of the gut microbiome on the genome and epigenome of colon epithelial cells: contributions to colorectal cancer development. Genome Med. 2019 Feb 25; 11(1): 11.
7) Fanny ER Vuik, Stella AV Nieuwenburg, Marc Bardou et al: Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years, Gut. 2019 Oct; 68(10): 1820-1826. Published online 2019 May 16. doi: 10.1136/gutjnl-2018-317592
8) Troeung L, Sodhi-Berry N, Martini A et al: Increasing

Incidence of Colorectal Cancer in Adolescents and Young Adults Aged 15-39 Years in Western Australia 1982-2007: Examination of Colonoscopy History. Front Public Health. 2017; 5(): 179.

9) Alan White, Lucy Ironmonger, Robert J. C. Steele et al: A review of sex-related differences in colorectal cancer incidence, screening uptake, routes to diagnosis, cancer stage and survival in the UK, Published online 2018 Sep 20. doi: 10.1186/s12885-018-4786-7

10) CRUK. Bowel cancer incidence statistics. 2017. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence#heading-One (Ref list)

11) Screening for colorectal cancer in African Americans: determinants and rationale for an earlier age to commence screening. Carethers JM Dig Dis Sci. 2015 Mar; 60(3):711-21.

12) Siegel R, Naishadham D, Jemal A , Cancer statistics, 2013. CA Cancer J Clin. 2013 Jan; 63(1): 11-30.

13) Wallace K, Hill EG, Lewin DN et al: Racial disparities in advanced-stage colorectal cancer survival, Cancer Causes Control. 2013 Mar; 24(3): 463-71.

14) American Cancer Society. Cancer facts and figures for Hispanics/Latinos 2012-2014. Atlanta, GA: American Cancer Society, 2012.

15) Nicholas J. Ollberding, Abraham M.Y. Nomura, Lynne R. Wilkens et al: Racial/Ethnic Differences in Colorectal Cancer Risk: The Multiethnic Cohort Study, Int J Cancer. Author manuscript; available in PMC 2012 Oct 15.

16) Nora B. Henrikson, Elizabeth M. Webber, Katrina A. Goddard et al: Family history and the natural history of colorectal cancer: systematic review, Genet Med. 2015 Sep; 17(9): 702–712. Published online 2015 Jan 15. doi: 10.1038/gim.2014.188

17) Jan T Lowery, Dennis J Ahnen, Paul C. Schroy III et al: Understanding the Contribution of Family History to Colorectal Cancer Risk and Its Clinical Implications: A State-of-the-Science Review, Cancer. 2016 Sep 1; 122(17): 2633–2645.

18) Alejandro Recio-Boiles; Burt Cagir., Colon Cancer, Treasure Island (FL): StatPearls Publishing; 2021 Jan-, Last Update: January 25, 2021.

19) Lodewijk A.A. Brosens, , G. Johan A. Offerhaus, M, and Francis M Giardiello, Hereditary Colorectal Cancer: Genetics and Screening, Surg Clin North Am. 2015 Oct; 95(5): 1067–1080. Published online 2015 Jun 16. doi: 10.1016/j.suc.2015.05.004

20) Lee J, Xiao YY, Sun YY et al: Prevalence and characteristics of hereditary non-polyposis colorectal cancer (HNPCC) syndrome in immigrant Asian colorectal cancer patients. BMC Cancer. 2017 Dec 13;17(1):843.

21) Porkka N, Lahtinen L, Ahtiainen M et al: Epidemiological, clinical and molecular characterization of Lynch-like syndrome: A population-based study. Int J Cancer. 2019 Jul 01;145(1):87-98

22) Sui QQ, Jiang W, Wu XD et al: A frameshift mutation in exon 19 of MLH1 in a Chinese Lynch syndrome family: a pedigree study. 2019 Jan.J Zhejiang Univ Sci B. 20(1):105-108.

23) Tarancón-Diez M, Büttner R, Friedrichs N. Enhanced Tumoral MLH1-Expression in MLH1-/PMS2-Deficient Colon Cancer Is Indicative of Sporadic Colon Cancer and Not HNPCC. Pathol Oncol Res. 2020 Jul; 26(3): 1435-1439

24) John T. Gay; Todd Troxell; Gary P. Gross.: Muir-Torre Syndrome, Treasure Island (FL): StatPearls Publishing; 2021 Jan-, Last Update: July 6, 2021.

25) Schierbeck J, Vestergaard T, Bygum A. Skin Cancer Associated Genodermatoses: A Literature Review. Acta Derm Venereol. 2019 Apr 01; 99(4): 360-369

26) Hu XR, Xu C, Kang Y et al: Correlation between mismatch-repair protein expression and clinicopathologic features in 658 colorectal cancers. Zhonghua Bing Li Xue Za Zhi. 2018 Nov 08; 47(11): 827-833.

27) Hampel H. Population Screening for Hereditary Colorectal Cancer. Surg Oncol Clin N Am. 2018 Apr; 27(2): 319-325

28) Kanth P, Grimmett J, Champine M, Burt R, Samadder NJ. Hereditary Colorectal Polyposis and Cancer Syndromes: A Primer on Diagnosis and Management. Am J Gastroenterol. 2017 Oct; 112(10): 1509-1525

29) Karstensen JG, Burisch J, Pommergaard HC et al: Colorectal Cancer in Individuals With Familial Adenomatous Polyposis, Based on Analysis of the Danish Polyposis Registry. Clin Gastroenterol Hepatol. 2019 Oct; 17(11): 2294-2300.e1

30) Sutcliffe EG, Bartenbaker Thompson A, Stettner AR et al: Multi-gene panel testing confirms phenotypic variability in MUTYH-Associated Polyposis. Fam Cancer. 2019 Apr; 18(2): 203-209

31) Lu Zhang and Jerry W. Shay, Multiple Roles of APC and its Therapeutic Implications in Colorectal Cancer

32) Sengupta S, Bose S. Peutz-Jeghers Syndrome. N Engl J Med. 2019 Jan 31; 380(5): 472

33) Eissing M, Ripken L, Schreibelt G et al: PTEN Hamartoma Tumor Syndrome and Immune Dysregulation. Transl Oncol. 2019 Feb; 12(2): 361-367

34) Craig Garofola; Zohaib Jamal; Gary P. Gross.: Cowden Disease, Treasure Island (FL): StatPearls Publishing; 2021 Jan-, Last Update: January 17, 2021.

35) Buecher B. Colorectal adenomatous polyposis syndromes: Genetic determinism, clinical presentation and recommendations for care. Bull Cancer. 2016 Feb; 103(2): 199-209

36) Ahmad Charifa; Radia T. Jamil; Xuchen Zhang: Gardner Syndrome, Treasure Island (FL): StatPearls Publishing; 2021 Jan-, Last Update: June 29, 2021.

37) D S Keller, A Windsor, R Cohen, M Chand : Colorectal cancer in inflammatory bowel disease: review of the evidence, Tech Coloproctol . 2019 Jan; 23(1): 3-13. doi: 10.1007/s10151-019-1926-2. Epub 2019 Jan 30.

38) Long AG, Lundsmith ET, Hamilton KE: Inflammation and Colorectal Cancer. Curr Colorectal Cancer Rep. 2017 Aug; 13(4): 341-351.

39) Favoriti P, Carbone G, Greco M et al: Worldwide burden of colorectal cancer: a review. Updates Surg. 2016 Mar; 68(1): 7-11.

40) Choi C.-H. R., Rutter M. D., Askari A., et al. Forty-year analysis of colonoscopic surveillance program for neoplasia in ulcerative colitis: an updated overview. The American Journal of Gastroenterology. 2015; 110(7): 1022-1034. doi: 10.1038/ajg. 2015.65

41) Keller DS, Windsor A, Cohen R, Chand M: Colorectal cancer in inflammatory bowel disease: review of the

evidence. Tech Coloproctol. 2019 Jan; 23(1): 3-13
42) Baker KT, Salk JJ, Brentnall TA, Risques RA - Precancer in ulcerative colitis: the role of the field effect and its clinical implications. Carcinogenesis. 2018 Jan 12; 39(1):11-20.
43) Sonnenberg A., Genta R. M. Epithelial dysplasia and cancer in IBD strictures. Journal of Crohn's and Colitis. 2015;9(9):769–775. doi: 10.1093/ecco-jcc/jjv108.
44) Fagunwa IO, Loughrey MB et al: Alcohol, smoking and the risk of premalignant and malignant colorectal neoplasms. Best Pract Res Clin Gastroenterol. 2017 Oct; 31(5): 561-568.
45) Punt CJ, Koopman M, Vermeulen L.. From tumour heterogeneity to advances in precision treatment of colorectal cancer. Nat Rev Clin Oncol. 2017; 144: 235-246.
46) Tsuyoshi Hamada, Jonathan A Nowak, Yohei Masugi et al: Smoking and Risk of Colorectal Cancer Sub-Classified by Tumor-Infiltrating T Cells, J Natl Cancer Inst. 2019 Jan; 111(1): 42-51.
47) Cheng J, Chen Y, Wang X et al: Meta-analysis of prospective cohort studies of cigarette smoking and the incidence of colon and rectal cancers. Eur J Cancer Prev. 2015 Jan; 24(1): 6-15.
48) Qiu F, Liang CL, Liu H et al: Impacts of cigarette smoking on immune responsiveness: Up and down or upside down? Oncotarget. 2017 Jan 3; 8(1):268-284.
49) Grando SA, Connections of nicotine to cancer., Nat Rev Cancer. 2014 Jun; 14(6): 419-29.
50) Xiang T, Fei R, Wang Z et al: Nicotine enhances invasion and metastasis of human colorectal cancer cells through the nicotinic acetylcholine receptor downstream p38 MAPK signaling pathway. Oncol Rep. 2016 Jan; 35(1): 205-10.
51) Efrat L. Amitay, Prudence R. Carr, Lina Jansen et al: Smoking, alcohol consumption and colorectal cancer risk by molecular pathological subtypes and pathways, Br J Cancer. 2020 May 26; 122(11): 1604-1610
52) Marco Rossi, Muhammad Jahanzaib Anwar, Ahmad Usman et al: Colorectal Cancer and Alcohol Consumption-Populations to Molecules, Cancers (Basel). 2018 Feb; 10(2): 38.
53) Varela-Rey M, Woodhoo A, Martinez-Chantar ML et all: Alcohol, DNA methylation, and cancer . Alcohol Res. 2013; 35(1): 25-35.
54) Bishehsari F., Magno E., Swanson G et al: Alcohol and gut-derived inflammation. Alcohol Res. Curr. Rev. 2017; 38: 163-171.
55) Moon JW, Lee SK, Lee YW et al: Alcohol induces cell proliferation via hypermethylation of ADHFE1 in colorectal cancer cells. BMC Cancer. 2014 May 28; 14():377.
56) Sun C, Wang FJ, Zhang HG et al: miR-34a mediates oxaliplatin resistance of colorectal cancer cells by inhibiting macroautophagy via transforming growth factor-β/Smad4 pathway, World J Gastroenterol. 2017 Mar 14; 23(10): 1816-1827
57) Bi YL, Mi PY, Zhao SJ et al: Salinomycin exhibits anti-angiogenic activity against human glioma in vitro and in vivo by suppressing the VEGF-VEGFR2-AKT/FAK signaling axis. Int J Mol Med. 2017 May; 39(5): 1255-1261.
58) A R Vieira,L Abar, DSM Chan et al: Foods and beverages and colorectal cancer risk: a systematic review andmeta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update ProjectAnn Oncol. 2017 Aug 1; 28(8): 1788-1802.
59) Cheng Zhang, Min Zhong: Consumption of beer and colorectal cancer incidence: a meta-analysis of observational studies. Cancer Causes Control (2015) 26: 549-560 DOI 10.1007/s10552-015-0532-5
60) Colditz GA & Peterson LL (2017) Obesity and cancer: evidence, impact and future directions. Clin Chem 64, 154-162.
61) Kyrgiou M, Kalliala I, Markozannes G et al. (2017) Adiposity and cancer at major anatomical sites: umbrella review of the literature. BMJ 356, j477.
62) Leila Abar, Ana Rita Vieira, Dagfinn Aune et al: Height and body fatness and colorectal cancer risk: an update of the WCRF–AICR systematic review of published prospective studies, Eur J Nutr 2017 DOI 10.1007/s00394-017-1557-1
63) Prudence R Carr, Efrat L Amitay, Lina Jansen et al: Association of BMI and major molecular pathological markers of colorectal cancer in men and women, The American Journal of Clinical Nutrition, Volume 111, Issue 3, March 2020, Pages 562-569, https://doi.org/10.1093/ajcn/nqz315
64) Pan Pan, Jianhua Yu, and Li-Shu Wang: Diet and colon: what matters?, Curr Opin Gastroenterol. 2019 Mar; 35(2): 101–106. doi: 10.1097/MOG.0000000000000501
65) Fred K. Tabung, Lisa S. Brown, and Teresa T. Fung. Dietary Patterns and Colorectal Cancer Risk: A Review of 17 Years of Evidence (2000-2016) Curr Colorectal Cancer Rep. 2017 017 Dec;13(6):440-454. doi: 10.1007/s11888-017-0390-5. Epub 2017 Oct 17.
66) Zheng X, Wu K, Song M et al: Yogurt consumption and risk of conventional and serrated precursors of colorectal cancer. Gut. 2020 May; 69(5): 970-972.
67) Gomes SD, Oliveira CS, Azevedo-Silva J et al: The Role of Diet Related Short-Chain Fatty Acids in Colorectal Cancer Metabolism and Survival: Prevention and Therapeutic Implications. Curr Med Chem. 2020; 27(24): 4087-4108.
68) Li YH, Niu YB, Sun Y et al, Role of phytochemicals in colorectal cancer prevention, World J Gastroenterol. 2015 Aug 21; 21(31): 9262-72.
69) Bylsma LC, Gillezeau C, Garawin TA et al: Prevalence of RAS and BRAF mutations in metastatic colorectal cancer patients by tumor sidedness: A systematic review and meta-analysis. Cancer Med. 2020 Feb; 9(3):1044-1057.
70) Jafar Nouri Nojadeh, Shahin Behrouz Sharif and Ebrahim Sakhinia, EXCLI J. 2018; 17: 159-168. Published online 2018 Jan 22. doi: 10.17179/excli2017-948
71) Manuela Porru, Luca Pompili, Carla Caruso et al: Targeting KRAS in metastatic colorectal cancer: current strategies and emerging opportunities, J Exp Clin Cancer Res. 2018; 37: 57.
72) Hisato Kawakami, Aziz Zaanan, and Frank A. Sinicrope , MSI testing and its role in the management of colorectal cancer, Curr Treat Options Oncol. Author manuscript; available in PMC 2016 Jul 1.
73) Cox AD, Fesik SW, Kimmelman AC et al: Drugging the undruggable RAS: Mission possible?, Nat Rev Drug Discov. 2014 Nov; 13(11): 828-51.
74) McCormick F, KRAS as a Therapeutic Target, Clin Cancer Res. 2015 Apr 15; 21(8): 1797-801.

75) Lavoie H, Gagnon J, Therrien M, ERK signalling: a master regulator of cell behaviour, life and fate. Nat Rev Mol Cell Biol. 2020 Oct; 21(10): 607-632.
76) Korzeniecki C, Priefer R, Targeting KRAS mutant cancers by preventing signaling transduction in the MAPK pathway. Eur J Med Chem. 2021 Feb 5; 211():1 13006.
77) Taieb J, Zaanan A, Le Malicot K et al:Mutations in patients with stage III Colon cancer, treated with Leucovorin, Fluorouracil, and Oxaliplatin with or without Cetuximab: A post Hoc Analysis of the PETACC-8 trial. JAMA Oncol. 2016 May 1; 2(5): 643-53.
78) Yaeger R, Cowell E, Chou JF et al: RAS mutations affect pattern of metastatic spread and increase propensity for brain metastasis in colorectal cancer. Cancer (Internet). 2015 Apr 15; 121(8): 1195-203
79) Lee SK, Hwang JH, Choi KY, Interaction of the Wnt/β-catenin and RAS-ERK pathways involving co-stabilization of both β-catenin and RAS plays important roles in the colorectal tumorigenesis. Adv Biol Regul. 2018 May; 68(): 46-54
80) Roberto M, Marchetti P, Arrivi G et al: The treatment paradigm of right-sided metastatic colon cancer: harboring BRAF mutation makes the difference. Int J Colorectal Dis. 2020 Aug; 35(8): 1513-1527

Corresponding Author:
Alexandra-Alina Vesa
Călugareni street, Nr.6, Ap.70, Oradea, Bihor county
Romania
Email: alexvesa92@yahoo.com
(Romania)