Role of dietary nutrients and metabolism in colorectal cancer

doi: 10.6133/apjcn.202403/PP.0001
Published online: March 2024

Running title: Nutrients and metabolism in colorectal cancer

Jinjun Ye MD, Xing Bao MD, Jiufeng Wei PhD, Yuanpeng Zhang MD, Yu Liu MD, Le Xin MD

Department of General Surgery, Longgang Central Hospital of Shenzhen, Longgang District, Shenzhen, Guangdong, China

Authors' email addresses and contributions:
JY: yejj610@163.com
Contribution: contributed to the study design, supervision of data collection, data analysis and interpretation, and writing the manuscript.

XB: 18567357@qq.com
Contribution: contributed to the study design, data analysis and interpretation, and reviewing the manuscript.

JW: asdwjf@163.com
Contribution: data analysis and interpretation, and reviewing the manuscript.

YZ: 393490649@qq.com
Contribution: data analysis and interpretation.

YL: aa8990976@163.com
Contribution: reviewing the manuscript.

LX: xinle1983@126.com
Contribution: conceived the study question, and contributed to the study design, supervision of data collection, and reviewing the manuscript.

Corresponding Author: Dr Le Xin, Department of General Surgery, Longgang Central Hospital of Shenzhen, No.6082 Longgang Avenue, Longgang District, Shenzhen, 518116, Guangdong, China. Tel:. Email: xinle1983@126.com

ABSTRACT

Colorectal cancer (CRC) is one of the most common malignancies and the leading causes of cancer related deaths worldwide. The development of CRC is driven by a combination of genetic and environmental factors. There is growing evidence that changes in dietary nutrition may modulate the CRC risk, and protective effects on the risk of developing CRC have been advocated for specific nutrients such as glucose, amino acids, lipid, vitamins, micronutrients and prebiotics. Metabolic crosstalk between tumor cells, tumor microenvironment components and intestinal flora further promote proliferation, invasion and metastasis of CRC cells and leads to treatment resistance. This review summarizes the research progress on CRC prevention, pathogenesis, and treatment by dietary supplementation or deficiency of glucose, amino acids, lipids, vitamins, micronutrients, and prebiotics, respectively. The roles played by different nutrients and dietary crosstalk in the tumor microenvironment and metabolism are discussed, and nutritional modulation is inspired to be beneficial in the prevention and treatment of CRC.

Key Words: colorectal cancer, risk factors, nutrient, metabolism, microenvironment

Colorectal cancer (CRC) is the third most common malignancy of the gastrointestinal tract worldwide and the second most prevalent cause of cancer death worldwide.[1] With changes in people's diets and lifestyles, millions of people die from CRC each year. Despite an overall decline in national CRC incidence and mortality due to advances in screening and treatment, an unexpected increase in CRC incidence in young adults has occurred.1 More than half of the cases and deaths could be attributed to modifiable risk factors such as smoking, unhealthy diet, heavy alcohol consumption, lack of physical activity and overweight, and therefore may be preventable.[2, 3]

Malnutrition and weight loss, affected by reduced intake, intestinal obstruction and malabsorption, are common in CRC patients, more than in patients with non-gastrointestinal tumors.[4] Cancers have been proven that malnutrition increases treatment toxicity, reduces quality of life and accounts for 10-20 % of deaths in cancer patients.[5] The etiology of CRC is not yet fully explained and the immediate causes remain unclear, but years of research have enabled us to distinguish many risk factors. The development of CRC is associated with non-modifiable risk factors, including age and genetic factors, as well as modifiable factors related to the environment and lifestyle.[6, 7, 8] It is now generally accepted that the development of CRC is the result of a combination of dietary, environmental, lifestyle and genetic factors.

Numerous studies have confirmed that obesity, poor dietary structure (lack of fruits and vegetables, frequent consumption of red and processed meat), excessive alcohol consumption, lack of physical activity, sedentary lifestyle, smoking and genetic factors are high risk factors for the development of colorectal cancer.[9] Of these, dietary factors are crucial risk factors and by changing diet and lifestyle habits, the risk of colorectal cancer can be effectively reduced. It is estimated that for every 50g processed meat consumed per day, the risk of developing CRC increases by approximately 16%, and for every 100g red meat consumed per day, the risk of developing CRC increases by approximately 12%.[10]

For CRC patients, nutritional interventions play an important role in their treatment, explaining the causal and protective role in the development of cancer.[11, 12] Therefore, rational and effective nutritional supplementation can reduce the damage to the organism caused by chemotherapy, prolong the survival of patients and improve life quality. This review focuses on the use and small-scale mechanisms of several nutrients (e.g., amino acids, sugars, lipids, vitamins, prebiotics, etc.) as CRC prevention strategies.

Regulation of nutrients

Malnutrition, metabolic abnormalities, immune imbalance and inflammatory responses are present throughout the course of tumor development, in which dietary nutrients play a key role. Radiotherapy affects the function of normal tissues surrounding the tumor; chemotherapy kills tumor cells while damaging normal cells, leading to immune dysregulation, malnutrition and other problems.[13] Nutritional preparations such as saccharides, amino acids, fatty acids, vitamins, microelement and prebiotics are available to improve malnutrition, metabolic and immune imbalance in patients.[14]

Dietary amino acids

Amino acids are the basic units that make up proteins and are involved in protein synthesis and energy metabolism, as well as in the growth and proliferation of tumor cells through several pathways. Some studies have shown a causal relationship between amino acid interventions and the incidence of CRC (Table 1).[15] Amino acid (AA) restriction can be used to target alterations in cancer cell metabolism, and dietary and pharmacological restriction of the sulfur-containing AAs methionine (Met) and cysteine (Cys) has been shown to have anti-cancer effects in colon cancer.[16, 17] Met, an essential amino acid for one-carbon metabolism, and dietary restriction of Met not only prolongs life-span and inhibit ageing-related disease processes, but also contributes to the inhibition of colon tumor development in rats at the early stages of carcinogenesis.[18] Met is a substrate for S-adenosylmethionine (SAM)

metabolism and is important for SAM-dependent downstream methylation reactions.[19] Adequate SAM is required to activate mechanistic target of rapamycin (mTORC1), the effector protein kinase of the pro-proliferative oncogenic signaling pathway.[20] Dysregulated amino acid sensing-induced mTORC1 activation drives chemotherapy resistance and colon tumorigenesis in mice, and restriction of leucine and cystine reverses drug resistance and leads to metabolic vulnerability.[21] Dietary and pharmacological restriction of serine (Ser) and glycine (Gly) in the one-carbon cycle has also shown anticancer activity in intestinal cancer.[22] Glucose via the Ser synthesis pathway is a fundamental process in cancer cells, promoting tumor growth. The availability and activation of Ser are largely dependent on phosphoglycerate dehydrogenase (PHGDH) catalyzing in serine synthesis.[23] In many cases, Ser synthesis is detrimental to cancer cells because it directs the glycolytic intermediate 3-phosphoglycerate (3-PG) away from glycolytic completion, thereby reducing energy production.[23] Ser synthesis from Glycine is harmful to cancer cells, and conversion of glycine to serine by the one carbon metabolizing enzyme serine hydroxymethyltransferase (SHMT) hinders efficient nucleotide synthesis, thereby affecting the rate of cell proliferation.[15, 24] These findings suggest that serine deprivation is a promising anti-cancer strategy. In addition, different metabolites of tryptophan modulate inflammatory bowel disease and CRC by affecting the immune system.[25] Dietary modulation of arginine (Arg) has also shown activity in CRC models.[26] A diet adapted to amino acids shows particular promise as a CRC prevention program and is a safe and beneficial dietary strategy.

Dietary glucose

High intakes of dietary carbohydrate may be associated with an increased risk of many health problems, such as intestinal diseases like CRC. Hyperglycemic diets, such as the Western diet, including refined carbohydrates (e.g., rice and noodles), may contribute to CRC risk through their hyperinsulinemia effects. The intake of sugar-sweetened beverage (SSBs) has increased significantly in recent decades, and the intake of monosaccharide, especially fructose, has increased dramatically.[27] High sugar intake contributes to insulin resistance, obesity and type 2 diabetes, which in turn promotes colorectal carcinogenesis.[28, 29] Growing evidence suggests that intake of sugary drinks in adulthood and teenagers contributes to increased risk of early-onset colorectal cancer in young people.[30] Total sugar intake is associated with higher levels of inflammatory and angiogenic biomarkers in CRC patients.[31]

Glucose is a key nutrient in a variety of metabolic pathways, including energy production, and is consumed by cancer cells to support their high proliferation rate.[32] Glucose contributes to

cancer progression, resistance to treatment and may even lead to the development of cancer. The majority of glucose entering cancer cells flows towards glycolysis and pyruvate synthesis. A portion of pyruvate enters the tricarboxylic acid (TCA) cycle via acetyl-CoA for Adenosine triphosphate (ATP) production in tumors.[33] The tendency of tumor cells to enhance anaerobic enzymes to produce lactate for energy is a phenomenon known as the Warburg effect, which illustrates how tumor cells rewire their metabolic program to meet their unique metabolic demands.[34] *In vivo,* insulin acts to effectively buffer blood glucose levels. However, insulin is also sensed by CRC tumor cells and expresses insulin receptor to activate the downstream of PI3K signaling pathway.[35] Abnormal PI3K activation is a signature of cancer, present in most cancer cells, and promotes tumor growth through positive regulation of cell cycle and anabolism. Insulin has been shown to inhibit Colorectal neoplasia differentially expressed (CRNDE) and Kallikrein 10 (KLK10), genes that drive aerobic glycolysis through PI3K/Akt/mTOR signaling pathway in CRC.[35, 36, 37] The role of the insulin in CRC carcinogenesis through direct cell proliferation and indirectly through altered glucose metabolism in tumor cells. Furthermore, chronically high levels of insulin, such as those found in obese and diabetic patients, are associated with a higher risk of CRC.[38] Many studies have demonstrated the benefits of a restricted diet for cancer treatment, with varying degrees of restriction in calorie intake leading to a reduction in blood glucose. Compared to obese individuals with low-calorie diets, high-calorie diets showed a significant increase in colon cell proliferation as assessed by stable isotope tracer method, making CRC a higher risk.[39] Therefore, a change in dietary structure such as glucose intake would be an ideal target to improve cancer treatment.

Dietary lipid

In a global evaluation, at least 12% CRC cases are directly attributed to overweight or obesity.40 A fat-rich diet is also a risk factor for obesity and cancer, and an extensive literatures describe a high dietary lipid intake leading to an increased risk of approximately 60% CRC, an effect that appears to be exerted in the colon.[41, 42] Intake of red meat and processed meat (sources of animal fat) is associated with CRC risk. CRC risk is higher in the high-fat intake group than in the low-fat intake group.[43] Although dietary lipid has been identified as a risk factor for CRC, the association between fatty acids and CRC is inconsistent. Different types of dietary lipid play different roles depending on their source, for example omega-3 polyunsaturated fatty acids (PUFAs) play a role in preventing inflammation in adipose tissue.[44] A positive association was found between total lipid, cholesterol, myristic

acid, valeric acid and high intake of palmitoleic acid with CRC, while heptanoic acid, oleic acid and low intake of palmitic acid were negatively associated with CRC, and these associations were stronger in subjects over 50 years of age.[41] PUFAs are classified into omega-3 and omega-6 families based on their functions and the location of double bonds. In general, omega-3 PUFAs inhibit tumor growth and metastasis, whereas omega-6 PUFAs exhibit the opposite effect.[45] Omega-6 PUFAs may promote the biosynthesis of immunosuppressive Prostaglandin E2 (PGE2) in the arachidonic acid pathway. However, omega-3 PUFAs were able to reduce the amount of PGE2, suggesting that the ratio of omega-6 to omega-3 may play an important role in CRC prevention.[46] It has also been found that omega-3 PUFAs may inhibit tumor growth by regulating the process of 5-methylcytosine (5mC) DNA methylation and 5-hydroxymethylocytosine.[47, 48] Moreover, an investigation of CRC risk and its association with different lipid types showed that CRC risk was higher in those with high saturated fat and cholesterol intakes.[49] Mechanistically, a high-fat diet may increase the risk of CRC, directly through its effects on inflammation, stem cell regulation and prostaglandin metabolism, and indirectly through its effects on the intestinal microbiota.[50] Therefore, rationalizing the diet and reducing the intake of dietary lipid, especially saturated and trans fatty acids, are promising strategies to reduce the risk of CRC recurrence and to reduce its development risk.

Dietary vitamins

Dietary vitamins are an important group of nutrients that can contribute to the health of the body in different ways. A meta-analysis from 13 cohort studies showed that total intake of vitamins A, C, E and folic acid from food showed a moderate negative association with CRC risk, and the combination of multiple vitamins showed a statistically significant negative association with CRC.[51] Among these mechanisms, the anti-inflammatory and immunomodulatory effects of vitamin D are particularly compelling, reducing CRC risk and mortality by inhibiting neoangiogenesis and cell proliferation and inducing apoptosis[52] In mice with inflammatory bowel disease (CRC risk factor), consumption of a high vitamin D diet reduced inflammation, suggesting that vitamin D may play an important role in inflammation-related carcinogenesis.[53] The B vitamins, including folate (B9), riboflavin (B2), pyridoxine (B6) and cobalamin (B12), are involved in one-carbon metabolism and play a vital role in the metabolism of sugars, lipids and proteins in the body. Studies have shown a U-shaped association between CRC risk and vitamin B6 intake, and an inverse U-shaped association between rectal cancer risk and vitamin B12.[54] Vitamin B2 intake and high blood

concentrations was inversely associated with CRC risk.[55] Moreover, dietary vitamin A supplementation in mice prior to tumor injection reduced the number of tumor cells in liver metastases caused by CRC.[56]

Abnormal DNA methylation is an early event in the development of colorectal cancer. Folic acid (B9) is essential for nucleotide synthesis and is essential for all cell types. Rapidly proliferating cells meet their need for new synthesized nucleotides for DNA replication and gene expression by consuming high levels of folate-targeted one-carbon metabolism.[15] 5-Methyltetrahydrofolate (THF), the major cytoplasmic form of folate, provides the carbon to methylate homocysteine to methionine to form SAM, the universal donor of methyl in DNA methylation.[57] Due to the role as a vector of single carbon groups and DNA methylation, inadequate folic acid intake is considered a possible cause of cancer.[15] The folate-dependent enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR) catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate.58 Methylenetetrahydrofolate (MTHFR) 677 C→T genotype is consistently negatively associated with colorectal cancer (CRC) risk and its association with adenoma risk.[58] Adequate vitamin B9 intake may prevent people from CRC with low Met intake.[54] In conclusion, it is well established that dietary vitamins have anti-cancer effects, but different vitamins are able to exert different effects in different situations (Table 2). Therefore, patients should take multivitamin supplement in their daily diet while undergoing oncology treatment.

Probiotic preparations

The composition of the microbial flora can be instrumental in creating favorable conditions for suppressing CRC. When the situation is reversed, ecological disturbance may appear, which can lead to problems with function and composition of intestinal microbiota, resulting in an immune stress response and inflammation, thereby exacerbating the risk of CRC.[59] An investigation with polyposis mice models showed that fiber intervention is an effective and safe method of reprogramming the microbiota to reduce colon tumorigenesis, and that a high fiber diet increased the expression of short-chain fatty acid producing bacteria and the butyrate receptor GPR109A, thereby inhibiting CRC.[60] The combination of *Lactobacillus acidophilus* and *Lactobacillus fermentum* reduces cell proliferation in CRC mice, demonstrating greater protection against intestinal tumorigenesis and supporting potential use as a biologic therapy for CRC prevention.[61] Resistant starch with anti-inflammatory and anti-cancer properties reduces tumor load in a rat model of colitis-associated CRC model by modulating microbial populations.[62] Probiotics are defined as live microorganisms that, when

given in adequate quantities, provide health benefits to the host. Probiotics may be involved in the prevention and treatment of CRC through three different mechanisms.[63] Firstly, probiotics inhibit the colonization of pathogenic bacterium through the release of antimicrobial peptides, reducing the luminal pH and competing directly with pathogens for nutrients[63, 64] Secondly, through unique immunomodulatory effects to reduce inflammation or enhance anti-tumor immunity.[63, 65] Finally, probiotics increase mucin production and expression of tight junction proteins and promote epithelial restoration to enhance intestinal barrier function.[63, 66] These findings suggest that microbial interventions are beneficial in the treatment of CRC.

Microelement

Cancer is inextricably linked to minerals in the body. Hydrogen sulfide produced in sulfur metabolism has been found to be a harmful by-product that may induce DNA damage, disrupt the mucus bilayer and promote inflammation and CRC.67 Studies of large cohorts have found that adherence to a sulfur-containing microbial diet is associated with an increased risk of CRC in relation to the relative abundance of sulfur-metabolizing gut bacteria, suggesting a potential mediating role for sulfur-metabolizing bacteria in the association between diet and CRC.[68]

Selenium is an essential micronutrient that plays a vital role in development and various physiological processes, and higher levels of selenium or selenium supplementation have antiviral effects.[69] A multicenter prospective cohort study showed that higher serum selenium levels were negatively associated with the risk of colorectal cancer, more significantly in women than men, and selenium levels below 80 μg/L may be a risk factor for CRC and, therefore that increased selenium intake may reduce the risk of CRC.[70]

Calcium is an essential mineral in the skeletal structure and is involved in cell differentiation and proliferation, as well as in intercellular junctions and signal transduction cascade responses, affecting cell cycle regulatory genes, which plays a key role in the pathogenesis of CRC.[71] Calcium obtained through diet is bound to bile acids at the intestinal level to obtain an insoluble form of calcium soap, which prevents cytotoxic effects caused by intestinal fatty acids and protects the integrity of the mucosa.[72]

Cancer patients rapidly develop many nutritional deficiencies due to inadequate food intake of micronutrients, reduced the ability of digesting and absorbing food and disturbance of body's internal balance.

Effects of nutritional deficiencies on the tumor microenvironment (TME)

The metabolism of tumor cells is highly sensitive to their environment. This phenomenon focuses attention from single nutrient to a complex network system that includes different nutrients and microbial components (Figure 1). TME is altered dynamically to support the high metabolic demands of neighboring tumor cells.[73] The communication between cancer cells and microenvironment facilitates their growth and evades immune surveillance.[74] The conversion of high concentrations of pyruvate to lactate in tumors is toxic and acidifies TME. The more glucose ingested, the more lactate produced, and high extracellular lactate displays the immunosuppressive function of cytotoxic T cells by reducing cytokine production and altering glycolysis.[75] The high glutamine depletion in cancer cells leads to glutamine deprivation in TME, which impairs the immune function of T cells.[76] Adipocytes increase the fatty acid oxidation pathway in CRC cells by upregulating CPT1A, which links adipocyte-mediated cellular metabolism to Wnt signaling in CRC cells, promoting β-catenin acetylation and activating the adipocyte-rich TME.[77] Homocysteine metabolism is a key amino acid associated with folic acid intake and folic acid depletion may increase homocysteine methylation of methionine, thereby reducing the production of glutathione required for DNA repair.[78]

Lack of nutrition and constant competition for glucose, glutamine, serine, methionine and tryptophan are associated with immunosuppressive properties. Thus, metabolic reprogramming in TME contributes to a pro-tumor immune environment and enables tumor cells to evade immune surveillance.

Nutrient utilization in metabolism

Nutrients, including carbohydrates, fatty acids, amino acids and vitamins, are essential for cellular homeostasis and macromolecular synthesis in the body and are processed through anabolism or catabolism pathways.[79] Catabolism produces energy by decomposing nutrients, while anabolism is the synthesis of complex macromolecules synthesized from simple molecules. Metabolism is essential for nutrient utilization and energy production.

One-carbon units, organic groups containing only one carbon atom, are produced during the catabolism of amino acids and are important substrates for nucleotide synthesis and methylation. As these groups cannot exist in free, they are usually carried by their carrier, tetrahydrofolate (THF), to participate in metabolic reactions, collectively known as one-carbon metabolism[80] One-carbon metabolism is composed of folate cycle and methionine cycle, with serine being the main source of one-carbon units. Serine/glycine biosynthesis and

one-carbon metabolism are essential for maintaining survival and rapid proliferation of cancer cells.[81] The serine synthesis pathway (SSP) represents a critical turning point in the conversion of glucose, where serine from *in vitro* uptake and *in vivo* glycolytic branch synthesis can be converted to glycine to provide one-carbon units for one-carbon metabolism, the over-activation of which drives tumorigenesis.[82] One-carbon metabolism is a complex network of circulating metabolism that supports the synthesis of porphyrins, thymine, purines, glutathione and SAM, which are important precursors for the synthesis of proteins, lipids, nucleic acids and other cofactors to maintain tumor growth.[83] In addition, one-carbon metabolism maintains the redox homeostasis of the tumor microenvironment and provides substrates for methylation reactions.

Aberrant fatty acid metabolic pathways have been reported to drive tumor development and progression, and are associated with poor prognosis in CRC patients.[84] Primary bile acids are synthesized in the liver, bound to taurine or glycine and released in the colon.[85] Subsequently they are decoupled by the bile salt hydrolases of the intestinal microbiota and converted to dangerous secondary bile acids by 7α-dehydroxylated bacteria.[86] Metabolomic analysis has confirmed elevated levels of secondary bile acids, including deoxycholic acid (DCA), in adenomas and intramucosal carcinomas.[87] In mice, DCA-induced alterations in the intestinal microbiota have been found to be accompanied by impaired intestinal barriers, low-grade inflammation and colon tumors.[88] DCA-induced ecological disturbance is characterized by an increased abundance of pathogenic bacteria and a decrease of beneficial bacteria, and such changes in the structure of the microbial community are sufficient in themselves to cause disease.

Conclusion

Diet is an integral part of a patient's daily life, and the development of CRC may be influenced by dietary structure other than genetic factors. People at high risk of CRC improve their quality of life, reduce CRC development by consuming dietary components that may prevent intestinal ecological and metabolic dysregulation, exert a regulatory effect on the tumor microenvironment, arrest the development of CRC. This article lists a large number of nutritional elements such as glucose, amino acids, fatty acids, vitamins, microelements and prebiotics on the development of CRC, as well as suggestions for adjusting dietary habits. The changes in metabolism produced by different nutrients in the body and thus the impacts on tumor development are revealed from the perspective of tumorigenesis and abnormal tumor metabolism. Dietary structure and metabolism are both variable factors affecting the

development of CRC. This article provides a more detailed understanding of their impact on CRC, and the combined analysis deepens the understanding of the overall picture and may lead to more favorable findings for the treatment of CRC. Dietary management for CRC patients is a complex and systematic project. In the future, more effective, reliable and safe methods are needed to guide clinical work and to better carry out research on dietary management of CRC patients.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

This study was supported by Shenzhen Science and Technology Innovation Committee (JCYJ20220530153813031).

REFERENCES

1. 1. Siegel RL, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC et al. Colorectal cancer statistics, 2020. CA Cancer J Clin. 2020;70: 145-64. doi: 10.3322/caac.21601
2. Islami F, Goding Sauer A, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ et al. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin. 2018;68: 31-54. doi: 10.3322/caac.21440
3. Des Guetz G, Uzzan B, Bouillet T, Nicolas P, Chouahnia K, Zelek L et al. Impact of physical activity on cancer-specific and overall survival of patients with colorectal cancer. Gastroenterol Res Pract. 2013;2013: 340851. doi: 10.1155/2013/340851
4. Chao X, Lei Z, Hongqin L, Ziwei W, Dechuan L, Weidong D et al. Faeces from malnourished colorectal cancer patients accelerate cancer progression. Clin Nutr. 2022;41: 632-44. doi: 10.1016/j.clnu.2022.01.001
5. Muscaritoli M, Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H et al. ESPEN practical guideline: Clinical Nutrition in cancer. Clin Nutr. 2021;40: 2898-913. doi: 10.1016/j.clnu.2021.02.005
6. Baena R, Salinas P Diet and colorectal cancer. Maturitas. 2015;80: 258-64. doi: 10.1016/j.maturitas.2014.12.017
7. Zhang Q, Luo H, Xun J, Ma Y, Yang L, Zhang L et al. Targeting PYCR2 inhibits intraperitoneal metastatic tumors of mouse colorectal cancer in a proline-independent approach. Cancer Sci. 2023;114: 908-20. doi: 10.1111/cas.15635
8. Li S, Keenan JI, Shaw IC, Frizelle FA Could Microplastics Be a Driver for Early Onset Colorectal Cancer? Cancers (Basel). 2023;15. doi: 10.3390/cancers15133323
9. Deng Y, Wang L, Huang J, Ding H, Wong MCS Associations between potential causal factors and colorectal cancer risk: A systematic review and meta-analysis of Mendelian randomization studies. J Dig Dis. 2022;23: 435-45. doi: 10.1111/1751-2980.13130

10. Schwingshackl L, Schwedhelm C, Hoffmann G, Knuppel S, Laure Preterre A, Iqbal K et al. Food groups and risk of colorectal cancer. Int J Cancer. 2018;142: 1748-58. doi: 10.1002/ijc.31198
11. Lewandowska A, Religioni U, Czerw A, Deptala A, Karakiewicz B, Partyka O et al. Nutritional Treatment of Patients with Colorectal Cancer. Int J Environ Res Public Health. 2022;19. doi: 10.3390/ijerph19116881
12. Wahlqvist ML Antioxidant relevance to human health. Asia Pac J Clin Nutr. 2013;22: 171-6. doi: 10.6133/apjcn.2013.22.2.21
13. Shirakami Y, Shimizu M, Kubota M, Araki H, Tanaka T, Moriwaki H et al. Chemoprevention of colorectal cancer by targeting obesity-related metabolic abnormalities. World J Gastroenterol. 2014;20: 8939-46. doi: 10.3748/wjg.v20.i27.8939
14. Vernia F, Longo S, Stefanelli G, Viscido A, Latella G Dietary Factors Modulating Colorectal Carcinogenesis. Nutrients. 2021;13. doi: 10.3390/nu13010143
15. Kanarek N, Petrova B, Sabatini DM Dietary modifications for enhanced cancer therapy. Nature. 2020;579: 507-17. doi: 10.1038/s41586-020-2124-0
16. Arensman MD, Yang XS, Leahy DM, Toral-Barza L, Mileski M, Rosfjord EC et al. Cystine-glutamate antiporter xCT deficiency suppresses tumor growth while preserving antitumor immunity. Proc Natl Acad Sci U S A. 2019;116: 9533-42. doi: 10.1073/pnas.1814932116
17. Gao X, Sanderson SM, Dai Z, Reid MA, Cooper DE, Lu M et al. Dietary methionine influences therapy in mouse cancer models and alters human metabolism. Nature. 2019;572: 397-401. doi: 10.1038/s41586-019-1437-3
18. Komninou D, Leutzinger Y, Reddy BS, Richie JP, Jr. Methionine restriction inhibits colon carcinogenesis. Nutr Cancer. 2006;54: 202-8. doi: 10.1207/s15327914nc5402_6
19. Mentch SJ, Mehrmohamadi M, Huang L, Liu X, Gupta D, Mattocks D et al. Histone Methylation Dynamics and Gene Regulation Occur through the Sensing of One-Carbon Metabolism. Cell Metab. 2015;22: 861-73. doi: 10.1016/j.cmet.2015.08.024
20. Gu X, Orozco JM, Saxton RA, Condon KJ, Liu GY, Krawczyk PA et al. SAMTOR is an S-adenosylmethionine sensor for the mTORC1 pathway. Science. 2017;358: 813-18. doi: 10.1126/science.aao3265
21. Solanki S, Sanchez K, Ponnusamy V, Kota V, Bell HN, Cho CS et al. Dysregulated Amino Acid Sensing Drives Colorectal Cancer Growth and Metabolic Reprogramming Leading to Chemoresistance. Gastroenterology. 2023;164: 376-91 e13. doi: 10.1053/j.gastro.2022.11.014
22. Muthusamy T, Cordes T, Handzlik MK, You L, Lim EW, Gengatharan J et al. Serine restriction alters sphingolipid diversity to constrain tumour growth. Nature. 2020;586: 790-95. doi: 10.1038/s41586-020-2609-x
23. Itoyama R, Yasuda-Yoshihara N, Kitamura F, Yasuda T, Bu L, Yonemura A et al. Metabolic shift to serine biosynthesis through 3-PG accumulation and PHGDH induction promotes tumor growth in pancreatic cancer. Cancer Lett. 2021;523: 29-42. doi: 10.1016/j.canlet.2021.09.007

24. Sanchez-Castillo A, Vooijs M, Kampen KR Linking Serine/Glycine Metabolism to Radiotherapy Resistance. Cancers (Basel). 2021;13. doi: 10.3390/cancers13061191

25. Ala M Tryptophan metabolites modulate inflammatory bowel disease and colorectal cancer by affecting immune system. Int Rev Immunol. 2022;41: 326-45. doi: 10.1080/08830185.2021.1954638

26. Satoh Y, Kotani H, Iida Y, Taniura T, Notsu Y, Harada M Supplementation of l-arginine boosts the therapeutic efficacy of anticancer chemoimmunotherapy. Cancer Sci. 2020;111: 2248-58. doi: 10.1111/cas.14490

27. Joh HK, Lee DH, Hur J, Nimptsch K, Chang Y, Joung H et al. Simple Sugar and Sugar-Sweetened Beverage Intake During Adolescence and Risk of Colorectal Cancer Precursors. Gastroenterology. 2021;161: 128-42 e20. doi: 10.1053/j.gastro.2021.03.028

28. Yu Z, Ley SH, Sun Q, Hu FB, Malik VS Cross-sectional association between sugar-sweetened beverage intake and cardiometabolic biomarkers in US women. Br J Nutr. 2018;119: 570-80. doi: 10.1017/S0007114517003841

29. Lee MS, Hsu CC, Wahlqvist ML, Tsai HN, Chang YH, Huang YC Type 2 diabetes increases and metformin reduces total, colorectal, liver and pancreatic cancer incidences in Taiwanese: a representative population prospective cohort study of 800,000 individuals. BMC Cancer. 2011;11: 20. doi: 10.1186/1471-2407-11-20

30. Hur J, Otegbeye E, Joh HK, Nimptsch K, Ng K, Ogino S et al. Sugar-sweetened beverage intake in adulthood and adolescence and risk of early-onset colorectal cancer among women. Gut. 2021;70: 2330-36. doi: 10.1136/gutjnl-2020-323450

31. Stewart KL, Gigic B, Himbert C, Warby CA, Ose J, Lin T et al. Association of Sugar Intake with Inflammation- and Angiogenesis-Related Biomarkers in Newly Diagnosed Colorectal Cancer Patients. Nutr Cancer. 2022;74: 1636-43. doi: 10.1080/01635581.2021.1957133

32. Abdel-Wahab AF, Mahmoud W, Al-Harizy RM Targeting glucose metabolism to suppress cancer progression: prospective of anti-glycolytic cancer therapy. Pharmacol Res. 2019;150: 104511. doi: 10.1016/j.phrs.2019.104511

33. Elia I, Rowe JH, Johnson S, Joshi S, Notarangelo G, Kurmi K et al. Tumor cells dictate anti-tumor immune responses by altering pyruvate utilization and succinate signaling in CD8(+) T cells. Cell Metab. 2022;34: 1137-50 e6. doi: 10.1016/j.cmet.2022.06.008

34. Fukushi A, Kim HD, Chang YC, Kim CH Revisited Metabolic Control and Reprogramming Cancers by Means of the Warburg Effect in Tumor Cells. Int J Mol Sci. 2022;23. doi: 10.3390/ijms231710037

35. Kasprzak A Insulin-Like Growth Factor 1 (IGF-1) Signaling in Glucose Metabolism in Colorectal Cancer. Int J Mol Sci. 2021;22. doi: 10.3390/ijms22126434

36. Ellis BC, Graham LD, Molloy PL CRNDE, a long non-coding RNA responsive to insulin/IGF signaling, regulates genes involved in central metabolism. Biochim Biophys Acta. 2014;1843: 372-86. doi: 10.1016/j.bbamcr.2013.10.016

37. Wei H, Dong C, Shen Z Kallikrein-related peptidase (KLK10) cessation blunts colorectal cancer cell growth and glucose metabolism by regulating the PI3K/Akt/mTOR pathway. Neoplasma. 2020;67: 889-97. doi: 10.4149/neo_2020_190814N758

38. Stefani C, Miricescu D, Stanescu S, II, Nica RI, Greabu M, Totan AR et al. Growth Factors, PI3K/AKT/mTOR and MAPK Signaling Pathways in Colorectal Cancer Pathogenesis: Where Are We Now? Int J Mol Sci. 2021;22. doi: 10.3390/ijms221910260

39. Magkos F, Sullivan S, Fitch M, Smith G, Fabbrini E, Mittendorfer B et al. Effect of Weight Gain and Weight Loss on In Vivo Colonocyte Proliferation Rate in People with Obesity. Obesity (Silver Spring). 2017;25 Suppl 2: S81-S86. doi: 10.1002/oby.21983

40. Whiteman DC, Wilson LF The fractions of cancer attributable to modifiable factors: A global review. Cancer Epidemiol. 2016;44: 203-21. doi: 10.1016/j.canep.2016.06.013

41. Seyyedsalehi MS, Collatuzzo G, Huybrechts I, Hadji M, Rashidian H, Safari-Faramani R et al. Association between dietary fat intake and colorectal cancer: A multicenter case-control study in Iran. Front Nutr. 2022;9: 1017720. doi: 10.3389/fnut.2022.1017720

42. MacLennan R MF, Bain C, Newland R, Russell A, Ward M, Wahlqvist. Effect of fat fibre and beta carotene intake on colorectal adenomas: further analysis of a randomized controlled dietary intervention trial after colonoscopic polypectomy. Asia Pacific Journal of Clinical Nutrition. 1999;8: 54-58. doi:

43. Kim M, Park K Dietary Fat Intake and Risk of Colorectal Cancer: A Systematic Review and Meta-Analysis of Prospective Studies. Nutrients. 2018;10. doi: 10.3390/nu10121963

44. May-Wilson S, Sud A, Law PJ, Palin K, Tuupanen S, Gylfe A et al. Pro-inflammatory fatty acid profile and colorectal cancer risk: A Mendelian randomisation analysis. Eur J Cancer. 2017;84: 228-38. doi: 10.1016/j.ejca.2017.07.034

45. Van Name MA, Savoye M, Chick JM, Galuppo BT, Feldstein AE, Pierpont B et al. A Low omega-6 to omega-3 PUFA Ratio (n-6:n-3 PUFA) Diet to Treat Fatty Liver Disease in Obese Youth. J Nutr. 2020;150: 2314-21. doi: 10.1093/jn/nxaa183

46. Ander BP, Edel AL, McCullough R, Rodriguez-Leyva D, Rampersad P, Gilchrist JS et al. Distribution of omega-3 fatty acids in tissues of rabbits fed a flaxseed-supplemented diet. Metabolism. 2010;59: 620-7. doi: 10.1016/j.metabol.2009.09.005

47. Huang Q, Wen J, Chen G, Ge M, Gao Y, Ye X et al. Omega-3 Polyunsaturated Fatty Acids Inhibited Tumor Growth via Preventing the Decrease of Genomic DNA Methylation in Colorectal Cancer Rats. Nutr Cancer. 2016;68: 113-9. doi: 10.1080/01635581.2016.1115526

48. Huang Q, Mo M, Zhong Y, Yang Q, Zhang J, Ye X et al. The Anticancer Role of Omega-3 Polyunsaturated Fatty Acids was Closely Associated with the Increase in Genomic DNA Hydroxymethylation. Anticancer Agents Med Chem. 2019;19: 330-36. doi: 10.2174/1871520618666181018143026

49. Tayyem RF, Bawadi HA, Shehadah IN, Abu-Mweis SS, Agraib LM, Bani-Hani KE et al. Macro- and micronutrients consumption and the risk for colorectal cancer among Jordanians. Nutrients. 2015;7: 1769-86. doi: 10.3390/nu7031769

50. O'Keefe SJ Diet, microorganisms and their metabolites, and colon cancer. Nat Rev Gastroenterol Hepatol. 2016;13: 691-706. doi: 10.1038/nrgastro.2016.165

51. Heine-Broring RC, Winkels RM, Renkema JM, Kragt L, van Orten-Luiten AC, Tigchelaar EF et al. Dietary supplement use and colorectal cancer risk: a systematic review and meta-analyses of prospective cohort studies. Int J Cancer. 2015;136: 2388-401. doi: 10.1002/ijc.29277

52. Kim H, Lipsyc-Sharf M, Zong X, Wang X, Hur J, Song M et al. Total Vitamin D Intake and Risks of Early-Onset Colorectal Cancer and Precursors. Gastroenterology. 2021;161: 1208-17 e9. doi: 10.1053/j.gastro.2021.07.002

53. Meeker S, Seamons A, Maggio-Price L, Paik J Protective links between vitamin D, inflammatory bowel disease and colon cancer. World J Gastroenterol. 2016;22: 933-48. doi: 10.3748/wjg.v22.i3.933

54. Bassett JK, Severi G, Hodge AM, Baglietto L, Hopper JL, English DR et al. Dietary intake of B vitamins and methionine and colorectal cancer risk. Nutr Cancer. 2013;65: 659-67. doi: 10.1080/01635581.2013.789114

55. Ben S, Du M, Ma G, Qu J, Zhu L, Chu H et al. Vitamin B(2) intake reduces the risk for colorectal cancer: a dose-response analysis. Eur J Nutr. 2019;58: 1591-602. doi: 10.1007/s00394-018-1702-5

56. Park EY, Pinali D, Lindley K, Lane MA Hepatic vitamin A preloading reduces colorectal cancer metastatic multiplicity in a mouse xenograft model. Nutr Cancer. 2012;64: 732-40. doi: 10.1080/01635581.2012.687425

57. Seol JE, Kim J, Lee BH, Hwang DY, Jeong J, Lee HJ et al. Folate, alcohol, ADH1B and ALDH2 and colorectal cancer risk. Public Health Nutr. 2020: 1-8. doi: 10.1017/S136898001900452X

58. Chiang FF, Huang SC, Wang HM, Chen FP, Huang YC High serum folate might have a potential dual effect on risk of colorectal cancer. Clin Nutr. 2015;34: 986-90. doi: 10.1016/j.clnu.2014.10.011

59. Molska M, Regula J Potential Mechanisms of Probiotics Action in the Prevention and Treatment of Colorectal Cancer. Nutrients. 2019;11. doi: 10.3390/nu11102453

60. Bishehsari F, Engen PA, Preite NZ, Tuncil YE, Naqib A, Shaikh M et al. Dietary Fiber Treatment Corrects the Composition of Gut Microbiota, Promotes SCFA Production, and Suppresses Colon Carcinogenesis. Genes (Basel). 2018;9. doi: 10.3390/genes9020102

61. Kahouli I, Malhotra M, Westfall S, Alaoui-Jamali MA, Prakash S Design and validation of an orally administrated active L. fermentum-L. acidophilus probiotic formulation using colorectal cancer Apc (Min/+) mouse model. Appl Microbiol Biotechnol. 2017;101: 1999-2019. doi: 10.1007/s00253-016-7885-x

62. Hu Y, Le Leu RK, Christophersen CT, Somashekar R, Conlon MA, Meng XQ et al. Manipulation of the gut microbiota using resistant starch is associated with protection against colitis-associated colorectal cancer in rats. Carcinogenesis. 2016;37: 366-75. doi: 10.1093/carcin/bgw019

63. Fong W, Li Q, Yu J Gut microbiota modulation: a novel strategy for prevention and treatment of colorectal cancer. Oncogene. 2020;39: 4925-43. doi: 10.1038/s41388-020-1341-1

64. Vogt SL, Serapio-Palacios A, Woodward SE, Santos AS, de Vries SPW, Daigneault MC et al. Enterohemorrhagic Escherichia coli responds to gut microbiota metabolites by altering metabolism and activating stress responses. Gut Microbes. 2023;15: 2190303. doi: 10.1080/19490976.2023.2190303

65. Klaenhammer TR, Kleerebezem M, Kopp MV, Rescigno M The impact of probiotics and prebiotics on the immune system. Nat Rev Immunol. 2012;12: 728-34. doi: 10.1038/nri3312

66. Pan M, Barua N, Ip M Mucin-degrading gut commensals isolated from healthy faecal donor suppress intestinal epithelial inflammation and regulate tight junction barrier function. Front Immunol. 2022;13: 1021094. doi: 10.3389/fimmu.2022.1021094

67. Ijssennagger N, van der Meer R, van Mil SWC Sulfide as a Mucus Barrier-Breaker in Inflammatory Bowel Disease? Trends Mol Med. 2016;22: 190-99. doi: 10.1016/j.molmed.2016.01.002

68. Wang Y, Nguyen LH, Mehta RS, Song M, Huttenhower C, Chan AT Association Between the Sulfur Microbial Diet and Risk of Colorectal Cancer. JAMA Netw Open. 2021;4: e2134308. doi: 10.1001/jamanetworkopen.2021.34308

69. Rayman MP Selenium and human health. Lancet. 2012;379: 1256-68. doi: 10.1016/S0140-6736(11)61452-9

70. Hughes DJ, Fedirko V, Jenab M, Schomburg L, Meplan C, Freisling H et al. Selenium status is associated with colorectal cancer risk in the European prospective investigation of cancer and nutrition cohort. Int J Cancer. 2015;136: 1149-61. doi: 10.1002/ijc.29071

71. Al-Ghafari AB, Balamash KS, Al DHA Relationship between Serum Vitamin D and Calcium Levels and Vitamin D Receptor Gene Polymorphisms in Colorectal Cancer. Biomed Res Int. 2019;2019: 8571541. doi: 10.1155/2019/8571541

72. Cruz-Pierard SM, Nestares T, Amaro-Gahete FJ Vitamin D and Calcium as Key Potential Factors Related to Colorectal Cancer Prevention and Treatment: A Systematic Review. Nutrients. 2022;14. doi: 10.3390/nu14224934

73. Li J, Ma X, Chakravarti D, Shalapour S, DePinho RA Genetic and biological hallmarks of colorectal cancer. Genes Dev. 2021;35: 787-820. doi: 10.1101/gad.348226.120

74. Lin A, Zhang J, Luo P Crosstalk Between the MSI Status and Tumor Microenvironment in Colorectal Cancer. Front Immunol. 2020;11: 2039. doi: 10.3389/fimmu.2020.02039

75. Nenkov M, Ma Y, Gassler N, Chen Y Metabolic Reprogramming of Colorectal Cancer Cells and the Microenvironment: Implication for Therapy. Int J Mol Sci. 2021;22. doi: 10.3390/ijms22126262

76. Cha YJ, Kim ES, Koo JS Amino Acid Transporters and Glutamine Metabolism in Breast Cancer. Int J Mol Sci. 2018;19. doi: 10.3390/ijms19030907

77. Mezrich JD, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, Bradfield CA An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. J Immunol. 2010;185: 3190-8. doi: 10.4049/jimmunol.0903670

78. Haas CB, Su YR, Petersen P, Wang X, Bien SA, Lin Y et al. Interactions between folate intake and genetic predictors of gene expression levels associated with colorectal cancer risk. Sci Rep. 2022;12: 18852. doi: 10.1038/s41598-022-23451-y

79. Kaur J, Debnath J Autophagy at the crossroads of catabolism and anabolism. Nat Rev Mol Cell Biol. 2015;16: 461-72. doi: 10.1038/nrm4024

80. Pan S, Fan M, Liu Z, Li X, Wang H Serine, glycine and one-carbon metabolism in cancer (Review). Int J Oncol. 2021;58: 158-70. doi: 10.3892/ijo.2020.5158

81. Xia Y, Ye B, Ding J, Yu Y, Alptekin A, Thangaraju M et al. Metabolic Reprogramming by MYCN Confers Dependence on the Serine-Glycine-One-Carbon Biosynthetic Pathway. Cancer Res. 2019;79: 3837-50. doi: 10.1158/0008-5472.CAN-18-3541

82. Ducker GS, Rabinowitz JD One-Carbon Metabolism in Health and Disease. Cell Metab. 2017;25: 27-42. doi: 10.1016/j.cmet.2016.08.009

83. Newman AC, Maddocks ODK One-carbon metabolism in cancer. Br J Cancer. 2017;116: 1499-504. doi: 10.1038/bjc.2017.118

84. Zhang Q, Deng T, Zhang H, Zuo D, Zhu Q, Bai M et al. Adipocyte-Derived Exosomal MTTP Suppresses Ferroptosis and Promotes Chemoresistance in Colorectal Cancer. Adv Sci (Weinh). 2022;9: e2203357. doi: 10.1002/advs.202203357

85. Di Ciaula A, Garruti G, Lunardi Baccetto R, Molina-Molina E, Bonfrate L, Wang DQ et al. Bile Acid Physiology. Ann Hepatol. 2017;16: s4-s14. doi: 10.5604/01.3001.0010.5493

86. Aguirre AM, Yalcinkaya N, Wu Q, Swennes A, Tessier ME, Roberts P et al. Bile acid-independent protection against Clostridioides difficile infection. PLoS Pathog. 2021;17: e1010015. doi: 10.1371/journal.ppat.1010015

87. Guo J, Pan Y, Chen J, Jin P, Tang S, Wang H et al. Serum metabolite signatures in normal individuals and patients with colorectal adenoma or colorectal cancer using UPLC-MS/MS method. J Proteomics. 2023;270: 104741. doi: 10.1016/j.jprot.2022.104741

88. Mouries J, Brescia P, Silvestri A, Spadoni I, Sorribas M, Wiest R et al. Microbiota-driven gut vascular barrier disruption is a prerequisite for non-alcoholic steatohepatitis development. J Hepatol. 2019;71: 1216-28. doi: 10.1016/j.jhep.2019.08.005

89. Yin XK, Wang YL, Wang F, Feng WX, Bai SM, Zhao WW et al. PRMT1 enhances oncogenic arginine methylation of NONO in colorectal cancer. Oncogene. 2021;40: 1375-89. doi: 10.1038/s41388-020-01617-0

90. Du F, Chen J, Liu H, Cai Y, Cao T, Han W et al. SOX12 promotes colorectal cancer cell proliferation and metastasis by regulating asparagine synthesis. Cell Death Dis. 2019;10: 239. doi: 10.1038/s41419-019-1481-9

91. Wong CC, Qian Y, Li X, Xu J, Kang W, Tong JH et al. SLC25A22 Promotes Proliferation and Survival of Colorectal Cancer Cells With KRAS Mutations and Xenograft Tumor Progression in Mice via Intracellular Synthesis of Aspartate. Gastroenterology. 2016;151: 945-60 e6. doi: 10.1053/j.gastro.2016.07.011

92. Hua Q, Zhang B, Xu G, Wang L, Wang H, Lin Z et al. CEMIP, a novel adaptor protein of OGT, promotes colorectal cancer metastasis through glutamine metabolic reprogramming via reciprocal regulation of beta-catenin. Oncogene. 2021;40: 6443-55. doi: 10.1038/s41388-021-02023-w

93. Chen X, Xu M, Xu X, Zeng K, Liu X, Pan B et al. METTL14-mediated N6-methyladenosine modification of SOX4 mRNA inhibits tumor metastasis in colorectal cancer. Mol Cancer. 2020;19: 106. doi: 10.1186/s12943-020-01220-7

94. Maddocks ODK, Athineos D, Cheung EC, Lee P, Zhang T, van den Broek NJF et al. Modulating the therapeutic response of tumours to dietary serine and glycine starvation. Nature. 2017;544: 372-76. doi: 10.1038/nature22056

95. Shi D, Wu X, Jian Y, Wang J, Huang C, Mo S et al. USP14 promotes tryptophan metabolism and immune suppression by stabilizing IDO1 in colorectal cancer. Nat Commun. 2022;13: 5644. doi: 10.1038/s41467-022-33285-x

96. Andersen V, Halekoh U, Bohn T, Tjonneland A, Vogel U, Kopp TI No Interaction between Polymorphisms Related to Vitamin A Metabolism and Vitamin A Intake in Relation to Colorectal Cancer in a Prospective Danish Cohort. Nutrients. 2019;11. doi: 10.3390/nu11061428

97. Yoon YS, Jung S, Zhang X, Ogino S, Giovannucci EL, Cho E Vitamin B2 intake and colorectal cancer risk; results from the Nurses' Health Study and the Health Professionals Follow-Up Study cohort. Int J Cancer. 2016;139: 996-1008. doi: 10.1002/ijc.30141

98. Holowatyj AN, Ose J, Gigic B, Lin T, Ulvik A, Geijsen A et al. Higher vitamin B6 status is associated with improved survival among patients with stage I-III colorectal cancer. Am J Clin Nutr. 2022;116: 303-13. doi: 10.1093/ajcn/nqac090

99. Wang F, Wu K, Li Y, Song R, Wu Y, Zhang X et al. Association of folate intake and colorectal cancer risk in the postfortification era in US women. Am J Clin Nutr. 2021;114: 49-58. doi: 10.1093/ajcn/nqab035

100. Boughanem H, Hernandez-Alonso P, Tinahones A, Babio N, Salas-Salvado J, Tinahones FJ et al. Association between Serum Vitamin B12 and Global DNA Methylation in Colorectal Cancer Patients. Nutrients. 2020;12. doi: 10.3390/nu12113567

101. Yun J, Mullarky E, Lu C, Bosch KN, Kavalier A, Rivera K et al. Vitamin C selectively kills KRAS and BRAF mutant colorectal cancer cells by targeting GAPDH. Science. 2015;350: 1391-6. doi: 10.1126/science.aaa5004

102. Dong Y, Liu Y, Shu Y, Chen X, Hu J, Zheng R et al. Link between risk of colorectal cancer and serum vitamin E levels: A meta-analysis of case-control studies. Medicine (Baltimore). 2017;96: e7470. doi: 10.1097/MD.0000000000007470

103. Ogawa M, Nakai S, Deguchi A, Nonomura T, Masaki T, Uchida N et al. Vitamins K2, K3 and K5 exert antitumor effects on established colorectal cancer in mice by inducing apoptotic death of tumor cells. Int J Oncol. 2007;31: 323-31. doi: 10.3892/ijo.31.2.323.

Table 1. Summary of the included studies of amino acids in colorectal cancer (CRC)

Kind	Model	Highlight	Authors
Arginine	Tumor from CRC patients and mouse	Arginine methylation promotes CRC cell proliferation, migration and invasion, and thus contributes to CRC progression.	Yin et al.[89]
Asparagine	Human CRC cells	Administration of L-asparaginase treatment significantly inhibits SOX12-mediated proliferation and metastasis of CRC cells.	Du et al.[90]
Aspartate	Tumor from CRC patients and mouse	SLC25A22 induces aspartate synthesis, mitogen-activated protein kinase and signal-regulated kinase activation to promote proliferation and migration in CRC cells and CRC tumors in mouse.	Wong et al.[91]
Glutamine	Human CRC cells	CEMIP induces CRC through reprogramming of glutamine metabolism, suggesting that combined inhibition of CEMIP and glutamine metabolism significantly attenuates CRC metastasis.	Hua et al.[92]
Lysine	Human CRC cells and tumor	Lysine-specific histone demethylase 5C-mediated demethylation of histone H3 lysine 4 trimethylation in the METTL14 promoter inhibits METTL14 transcription, thus suppressing CRC cell migration, invasion and metastasis.	Chen et al.[93]
Methionine	Mouse	Dietary restriction of methionine affects therapeutic response in colorectal cancer mice through controlled and reproducible changes in single-carbon metabolism.	Gao et al.[17]
Serine	Mouse	Dietary restriction of serine and glycine reduces tumor growth in mouse models of pancreatic and intestinal cancer by antagonizing antioxidant responses.	Oliver et al.[94]
Tryptophan	Mouse	Pharmacological targeting of USP1 reduces IDO1 expression, reverses cytotoxic T cell suppression and tryptophan metabolism, increases responsiveness to anti-PD-38, and exerts immunotherapeutic effects against CRC.	Shi et al.[95]

CRC, colorectal cancer; SOX12, sex-determining region Y-box (SOX) 12; SLC25A22, solute carrier family 25 member 22; CEMIP, cell migration inducing hyaluronidase 1; METTL14, methyltransferase 14; USP1, ubiquitin specific peptidase 1; IDO1, indoleamine 2,3-dioxygenase 1; anti-PD-38, Anti-programmed cell death protein 38

Table 2. Summary of the included studies of vitamins in CRC

Vitamin	Model	Highlight	Authors
A	Clinical cohort	Dietary supplements of vitamin A were not found to be associated with CRC risk.	Andersen et al. [96]
B2	Clinical cohort	Data on the dietary addition of vitamin B2 do not support its beneficial effect in reducing the incidence of CRC.	Yoon et al. [97]
B6	Clinical cohort	Higher preoperative vitamin B6 status is associated with improved overall survival in patients with stage I-III CRC.	Holowatyj et al. [98]
B9	Clinical cohort	Total folic acid intake is associated with a lower overall CRC risk after a long latency period.	Wang et al.[99]
B12	Clinical cohort	LINE12 methylation in tumor and peripheral blood mononuclear cells was lower in the high vitamin B12 group, suggesting that vitamin B12 may be associated with or mediate the epigenetic status of CRC	Boughanem et al.[100]
C	CRC cell lines	Vitamin C selectively kills KRAS and BRAF mutated CRC cells by targeting GAPDH and has therapeutic use in CRC.	Yun et al.[101]
D	Clinical cohort	Higher total vitamin D intake was associated with decreased risks of early-onset CRC and precursors.	Kim et al.[52]
E	Clinical cohort	CRC associated with low serum vitamin E concentrations.	Dong et al.[102]
K	Colon 26 cells	Vitamins K2, K3 and K5 exert effective anti-tumor effects against colorectal cancer in vitro and in vivo by inducing cysteine-dependent apoptotic death of tumor cells.	Ogawa et al.[103]

CRC, colorectal cancer; LINE12, long interspersed nuclear element 12; KRAS, Kirsten rat sarcoma viral oncogene; BRAF, B-Raf proto-oncogene; GAPDH, glyceraldehyde 3-phosphate dehydrogenase.

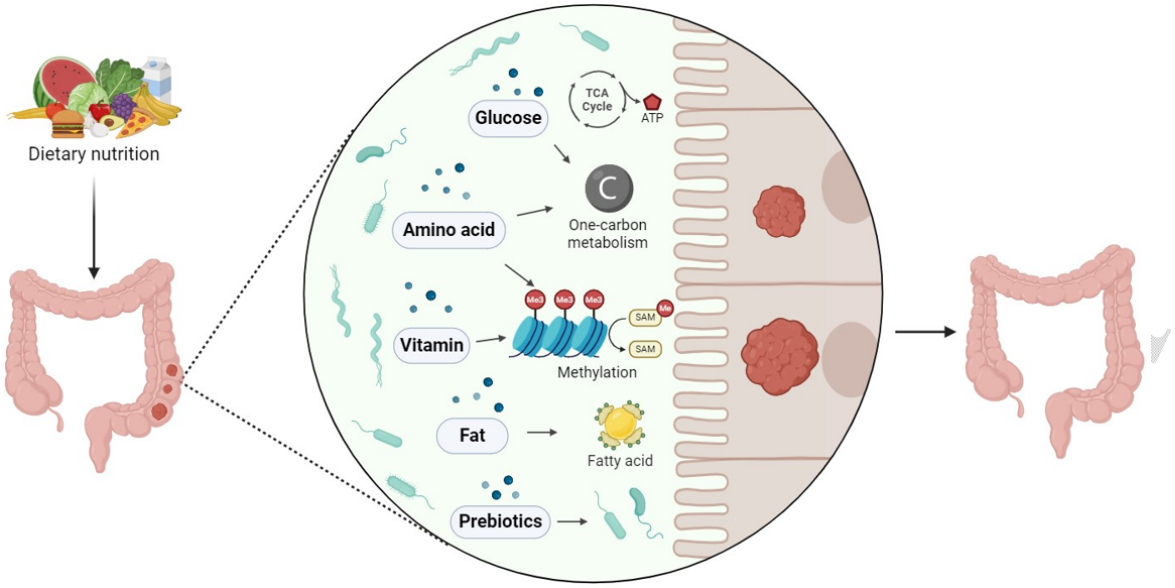

Figure 1. The role of dietary nutrients in colorectal carcinogenesis. Glucose promotes colorectal cancer via the tricarboxylic acid cycle and PI3K/Akt/mTOR pathway.[33, 35, 36, 37] Amino acids, vitamins, fatty acids promote tumorigenesis via S-adenosylmethionine-dependent methylation.[15, 19, 20, 47, 48, 58] Glucoses, amino acids, vitamins contribute to colorectal cancer development through one-carbon metabolism.[15, 22, 24, 57] Fatty acids, prebiotics promote inflammation by affecting gut microorganisms.[50, 61, 62] The figure was created with BioRender.com..