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Can Dietary Iron Bioavailability Influence Colorectal Cancer Risk and Prognosis?

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Abstract

Colorectal cancer (CRC) stands apart from other malignancies due to its pronounced association with dietary patterns. Approximately 70% of all CRC cases arise sporadically, and suboptimal dietary and lifestyle choices can override certain predisposing factors, including a family history of the disease. Hitherto, the most compelling evidence linking CRC risk has been attributed to heme iron, predominantly found in red and processed meats, although this form of iron constitutes a mere 20% of total dietary iron. The human organism maintains a remarkably intricate and tightly regulated iron homeostasis system owing to the deleterious consequences of both excessive and deficient serum iron levels. Dietary sources remain the sole means to replenish iron losses. Despite the abundant presence of iron in various food sources, its absorption, commonly referred to as bioavailability, is notably restricted due to an array of dietary inhibitors and homeostatic mechanisms.

Consequently, a substantial 80% of ingested dietary iron is excreted in fecal matter, resulting in fecal iron concentrations that surpass those found in most body tissues by a tenfold margin. Prolonged exposure of the colorectum to excessive fecal iron, combined with concurrent physiological alterations, can instigate oncogenic processes leading to CRC. Notably, despite their recognized significance in CRC pathology, dietary habits, and lifestyle factors have been sporadically integrated into predictive models, primarily concerning CRC recurrence. Nonetheless, these models exhibit disparities in the dietary components, rendering them non-universally applicable. In light of these disparities, postulating that incorporating bioavailable iron, in conjunction with hepcidin levels, may offer superior predictive value for CRC risk assessment, and herein, elucidates the scientific foundation supporting this hypothesis.

Keywords: Colorectal neoplasms, Dietary iron, Biological availability, Hepcidins, Projections and predictions

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The Burden of Colorectal Cancer

In Europe, 4.4 million people annually are diagnosed with cancer, with 1.96 million cancer-related deaths, 12.5% of which are attributed to colorectal cancer (CRC).[1] The toll of cancer is experienced by the entire society, either directly or indirectly. For example, the global annual healthcare allocation for cancer patients is around € 900 billion.[2] Europe's Beating Cancer Plan under the motto "Let's Strive for More" was presented at the European Parliament on World Cancer Day (4 February 2020). This European project has settled four plan pillars: prevention, early diagnosis, treatment, and follow-up care.[2]

The burden of cancer in 27 countries of the European Union (EU) in 2020 has risen to 2.7 million new cases and 1.3 million deaths consequently. CRC is the second most common cancer (11.8% of all new cases) and the second cause of death (12.5% of all cancer deaths), with high mortality rates, especially in Eastern countries.[3] Globally, CRC is the third most common cancer.[4]

Today's trends in incidence and mortality strongly correlate with the Human Development Index (HDI; a summary measure of a country's social and economic development based on mean years of education, expected years of education, life expectancy at birth, and the gross national income per capita), so not surprisingly, rates are stable or declining in most of the developed countries of the world.[1] Nevertheless, the incidence of CRC steadily grows in people aged 50 or older.[1] Early CRC diagnosis is crucial for survival.[4]

In countries that implemented early detection programs in the 1990s, the decline in incidence and mortality rates has been recorded nowadays, even in high-risk age groups. However, many of the national programs are underperforming. If the response rates were 45%, there could finally be a 15% reduction in mortality rates due to CRC. Many countries have not reached this goal. Response rates vary widely across the EU, from 71.3% in the Netherlands to 16.7% in Poland for both genders and age groups aged 50 or older.[5]

Men have a higher incidence of CRC in comparison with women (10.6% vs. 9.2%),[6] while on the other hand, women tend to have more prolonged survival (58.7% vs. 59.2%) and lower mortality rates (6.3% vs. 8.8%) in comparison with men. This; however, changes in women over 50 years,[7] probably because of the changes in the sex hormone in menopause.[8] Also, women are more likely to have the so-called right (proximal) CRC, a more aggressive form concerning the left (distal) CRC, which is more common in men.[7] The distribution of sporadic CRC, along with their main characteristics, is illustrated in figure 1, and for more information about the difference between left and right-sided CRC, please consult.[9]

Recognized Risk Factors for CRC

Most CRC cases (70%) are spontaneous, and 10 to 30% of CRCs are hereditary.[10] Lynch syndrome is the most common hereditary cancer to correlate with an increased risk, not only for CRC, but also for endometrium, ovary, and stomach cancer.[11] Juvenile tumours are estimated to be related to hereditary CRC syndromes.[12] Yet, the risk of CRC increases with other diagnoses, such as acromegaly,[13] ulcerative colitis and Crohn's disease,[14] acute diverticulitis,[15] cystic fibrosis,[16] diabetes,[17] insulin therapy,[18] and immunosuppressants administration.[19] This review focuses solely on spontaneous CRC. For more information about hereditary CRC, please refer to other references.[20, 21]

What distinguishes CRC from all other cancers is its high association with diet.[22] Poor diet and lifestyle habits can overcome positive genetic family history or diagnosis of some inflammatory bowel diseases.[23] The latest available data on the impact of diet and lifestyle on CRC (risk and progression) are shown in table 1. The strongest correlation was found for the consumption of processed and red meat, that is, heme iron (Fe),[24] while for the total dietary intake of Fe, the results are inconsistent.[25-31]

Daily consumption of 50 g of processed meat (salted and smoked meat, e.g., sausages, kulen (op. a. traditional smoked sausage made from pork meat with red paprika), dry-cured ham or

Table 1. Role of diet and lifestyle habits on CRC risk and progression[32]

	Convincing	Probable	Limited suggestive
Decreases risk	Physical activity	Whole grains Foods containing dietary fiber Milk and dairy Calcium supplements (consumption >200 mg/day)	Foods containing vitamin C (only for colon cancer) Fish Vitamin D (status, foods and supplements) Multivitamin supplements**
Increases risk	Processed meat Alcohol (>30 g/day or 2 drinks) Body fatness (observed through BMI, waist circumference, and waist-to-hip ratio) Adult attained height*	Red meat	Low intake of non-starchy vegetables (<100 g/day) Low intake of fruits (<100 g/day) Foods that contain heme iron

*Adult attained height is believed to have a role in carcinogenesis due to growth hormone, but the effect is not direct; **The definitions and categories regarding supplements and not standardized; CRC: Colorectal cancer; BMI: Body mass index

bacon) increases the risk of CRC by 18%.[24] Red meat (beef, pork, and game meat) increases the risk by 12%.[33] The negative impact is attributed to the high content of heme Fe, nitrates, and nitrites used in producing these products (especially industrial meat products) and components from the smoke, which means that the same danger lies in domestic cured meat products.[10] However, a recent and pervasive study consisting of four systematic reviews[34] did not conclude the need to reduce the consumption of red and/or processed meat, primarily due to poor evidence quality.

Dietary Sources and Bioavailability of Iron

All cells highly depend on iron, but this is even more pronounced for cancer cells because they are iron-dependent.[35] Iron homeostasis is a very complex process because of the potentially detrimental effects of Fe in both low and high concentrations.[36, 37] Daily loss of Fe ranges from 1 mg (0.8 mg for adult males and 0.9 mg for adult, non-menstruating women) to more than 2.0 mg in menstruating women.[36] The loss of Fe is exclusively recovered through diet, i.e., via absorption of dietary Fe (by enterocytes in the proximal duodenum). Iron absorption is kept low to avoid potentially detrimental effects.[36, 38] Generally, Fe absorption varies significantly depending on the dietary sources. It will depend on the form in which Fe is present in specific foods and the number of inhibitors widely abundant in foods, which could lower its bioavailability.[36] Not only that, an individual's Fe status significantly alters the absorption, being higher in anemic or Fe-deficient persons.[39] At this point, a crucial role of Fe bioavailability lies in a small peptide synthesized in the liver, hepcidin. Hepcidin regulates the absorption of Fe by complex mechanisms, and many factors induce synthesis.[40]

Iron in foods is present as heme or non-heme Fe iron.[41] Heme Fe is primarily found in foods of animal origin, especially red meat, whose bioavailability ranges between 15% and 35%. Nevertheless, its contribution to the total dietary intake of Fe is only around 20%.[10]

On the other hand, non-heme Fe, which is primarily found in foods of plant origin, accounts for the remaining 80% of the total dietary Fe intake.[10, 41] Non-heme Fe has low bioavailability (2%-20%) due to several potent inhibitors present in a variety of foods.[42] The best-known Fe bioavailability promotors are ascorbic acid and meat proteins.[42] Some of the inhibitors of Fe bioavailability include phytic and oxalic acid, starch (acts similarly to phytates), polyphenols and tannins from coffee and tea, phosphates and phosphoproteins from egg white and milk, other minerals, antacids and other drugs that reduce gastric secretion.[42] The best animal and plant food sources of Fe, along with the amount of Fe being absorbed and its known absorption inhibitors, are presented in table 2. Still, one must remember that the values provided in the table are for sole foods, and complex diets will result in variable Fe bioavailability, primarily due to various nutrient-nutrient interactions that may act synergistically.

Interestingly, some of the most potent inhibitors

of Fe absorption[42] are closely related to the so-called "low-risk" (protective) diet for CRC, with particular emphasis on phytic acid from whole grains and calcium (Ca) from milk and dairy products (Table 1). Although both show a dose-dependent inhibitory effect, Ca is the only one that inhibits both heme and non-heme Fe.[36] These Fe-Ca complexes are exceptionally "inert." If the amount of Ca in a meal is < 50 mg, there is no inhibiting effect on Fe, while the maximum inhibition is achieved, if Ca content in a meal is 300-600 mg.[42] Importantly, the inhibiting effect of Ca on Fe bioavailability is the same regardless of the source (from milk and dairy or supplements), and daily intake of Ca ≥ 700 mg reduces the risk of CRC by 22%, especially for distal cancer.[32, 43] At the same time, Ca has been shown to act protectively on the recurrence at 36 to 60 months from the initial diagnosis.[44]

The gastric function is vital in Fe bioavailability, primarily gastric acidity.[38] Heme Fe absorption is not influenced by gastric pH,[36] but non-heme Fe comes in two primary forms, soluble ferrous (Fe^{2+}) and insoluble ferric (Fe^{3+}) ion. The latter easily forms complexes with other anions and requires pH < 3.[41] Gastrin, a peptide hormone that stimulates the secretion of gastric acid, plays an important role not only in Fe homeostasis (binds two ferrous ions) through interaction with transferrin (a Fe transport protein in the blood) but is also a potent cell proliferating factor for all cells in the digestive tract.[38] All conditions impairing gastric function (gastritis diagnosis) will affect Fe absorption. Besides medications, specific infection agents spark interest,[45] particularly Helicobacter pylori (H. pylori) infection.[46] H. pylori was confirmed to directly increase the risk of CRC directly, probably via increased gastrin secretion.[46, 47]

Iron Homeostasis in the Body

Absorption mechanisms of non-heme Fe are well known; the exact mechanisms are still not wholly elucidated for heme Fe.[35-37] Briefly, upon absorption in the enterocytes, Fe is transported by transferrin to all cells and tissues (Fe is imported into the cells via transferrin receptors). At the same time, surplus Fe is stored in the liver (primarily as ferritin, the major Fe storage protein). The master regulator of Fe homeostasis is hepcidin, a hormone that negatively regulates Fe absorption. Hepcidin regulates Fe absorption via

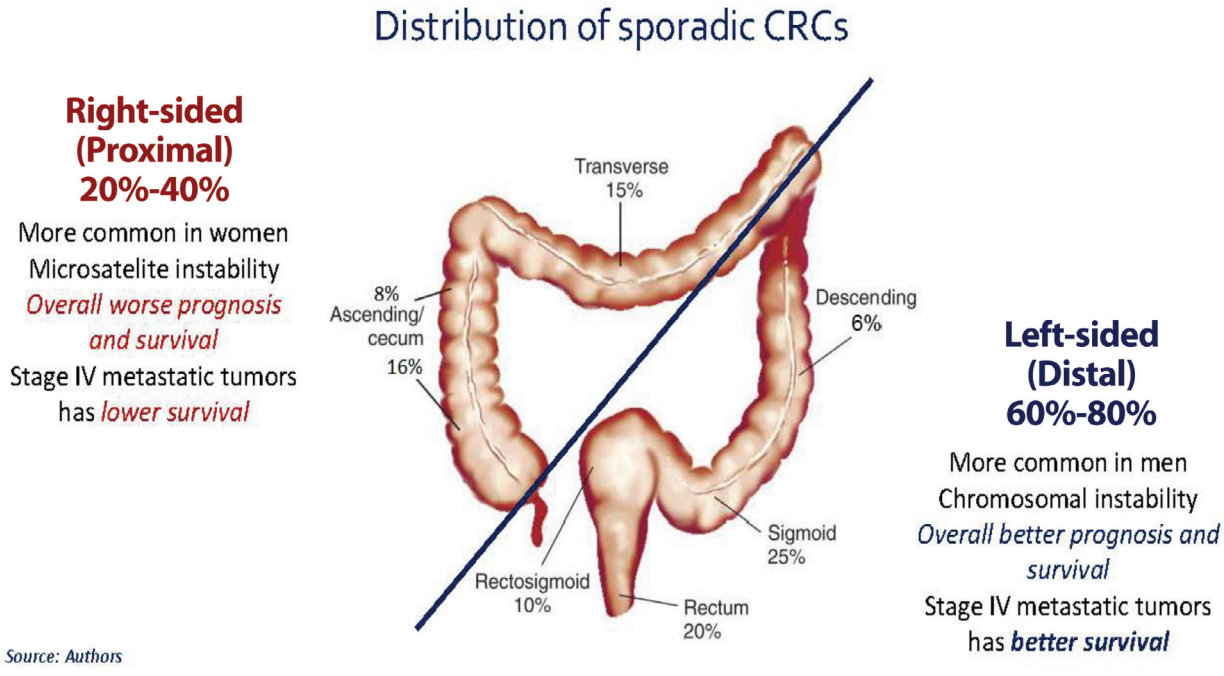

Figure 1. This figure illustrates the distribution of sporadic colorectal cancer.
CRC: Colorectal cancer

Table 2. Content and bioavailability of iron from selected food sources of animal and plant origin

Food source*		Content (per 100 g)[48]					Iron available for absorption[49, 50§]	Additional nutrients (amount per 100 g of food) that negatively affect iron absorption
		Iron (mg)	Calcium (mg)	Vitamin C (mg)	Vitamin B12 (µg)	Total dietary fiber (g)		
Red meat	Beef, lean, raw	1.77	18	0.0	1.47	0.0	50% heme	None[42]
	Lamb (leg), lean, raw	1.82	6	0.0	2.70	0.0		
	Pork, lean, raw	0.00	17	0.6	0.66	0.0	25% heme	
White meat	Chicken, breasts	0.37	5	0.0	0.27	0.0	5-10% overall	None[42]
	Chicken, dark meat	1.03	12	3.1	0.36	0.0		
Fish	Tuna, bluefin	1.02	8	0.0	9.43	0.0	18-93%[51]	None[42]
	Salmon, farmed	0.34	9	3.9	3.23	0.0		
	Trout, farmed	0.31	25	2.9	4.30	0.0		
Milk and dairy	Milk, 3.25% fat	0.03	113	0.0	0.45	0.0	0%	No inhibition at Ca content <50 mg[42]
	Yogurt, Greek, plain	0.00	100	0.0	0.75	0.0		
	Cheese, mozzarella	0.44	505	0.0	2.28	0.0		
	Cheese, Gouda	0.24	700	0.0	1.54	0.0		
	Egg, whole, raw	1.75	56	0.0	0.89	0.0		27% reduction[42]
Legumes and cereals	Lentils, cooked	3.33	19	1.5	0.00	7.9		0.27–1.51 g PA[54]
	White beans, cooked	3.7	90	90.0	0.00	6.3	3.2%[52]	1.41% PA[55]
	Red kidney beans, cooked	2.94	1.2	28.0	0.00	7.4	3.2%[52]	0.61–2.38 g PA[54]
	Quinoa, cooked	1.49	17	0.0	0.00	2.8		1.18 g PA[56]
	Brown rice, cooked	0.56	3	0.0	0.00	1.6		0.89 g PA[56]
	Oats, raw	4.25	52	0.0	0.00	10.1		0.42–1.16 g PA[54]
Vegetables	Spinach, raw	2.71	99	28.1	0.00	2.2	1.7%[52]	326-563 mg OA;[57] 119 mg polyphenols[58]
	Spinach, cooked	3.18	116	23.1	0.00	2.6	1.7% /8.4%[53]	
	Broccoli, cooked	0.76	49	78.7	0.00	2.9		40-100 mg polyphenols[5]
	Kale, cooked	1.72	272	70.1	0.00	4.4	11.0%[53]	15-34 mg OA;[57] 300-600 mg polyphenols[58]
	Pepper, raw	0.37	9	97.0	0.00	1.8		0.11% PA;[55] 5-10 mg polyphenols[58]
	Tomatoes, raw	0.27	10	13.7	0.00	1.2		0.11% PA;[55] 2-15 mg polyphenols[58]
	Mushrooms, cooked	1.74	6	4.0	0.00	2.2		0.11±0.01 mg PA; 0.41±0.03 tannins[59]
Fruits	Strawberries, raw	0.41	16	58.8	0.00	2.0		0.07% PA;[55] 235 mg polyphenols[58]
	Raisins	1.79	62	2.3	0.00	4.5		0.18% PA;[55] 30-175 mg polyphenols[58]
	Figs, raw	0.37	35	2.0	0.00	2.9		0.07% PA[55]
	Figs, dried	2.03	162	1.2	0.00	9.8		0.80% PA[55]
	Apricots, dried	2.66	55	1.0	0.00	7.3		0.70% PA;[55] 25-50 mg polyphenols[58]
	Prunes	0.93	43	0.6	0.00	7.1		0.12% PA;[55] 20-250 mg polyphenols[5]
Nuts and seeds	Hazelnuts	4.7	114	6.3	0.00	9.7		0.92% PA;[55] 495 mg polyphenols[58]
	Walnuts	2.91	98	1.3	0.00	6.7		0.20–6.69 g PA[54] /0.63% PA;[55] 28 mg polyphenols[58]
	Sesame seeds	6.36	60	0.0	0.00	11.6		1.44–5.36 g PA[54] /4.71% PA[55]
	Pumpkin seeds	8.07	52	1.8	0.00	6.5		4.90% PA[55]
Other products	Soy milk	0.42	123	0.0	0.85**	0.2		10.7% PA;[55] 30-175 mg polyphenols[58]
	Tofu, raw, regular	5.36	350	0.1	0.00	0.3		10.7% PA;[55] 42 mg polyphenols[58]
	Tahini	8.95	426	0.0	0.00	9.3		

PA: Phytic acid; OA: Oxalic acid; *: Beef (NDB# 23651), Lamb (NDB# 17013), Pork (NDB# 10228), Chicken (NDB# 5062 and 5043), Tuna (NDB# 15117), Salmon (NDB# 15236), Trout (NDB# 15240), Milk (NDB# 1211), Yoghurt (NDB# 1293), Cheese (NDB# 1026 and 1022), Egg (NDB# 1123), Lentils (NDB# 16070), White beans (NDB# 16350), Kidney beans (NDB# 16033), Quinoa (NDB# 20137), Brown rice (FDC ID: 1101631), Oats (FDC ID: 1101825), Spinach (FDC ID: 1103136 and 1103137), Broccoli (FDC ID: 1103172), Kale (FDC ID: 1103117), Pepper (FDC ID: 1103370), Tomatoes (FDC ID: 1103276), Mushrooms (NDB# 11261), Strawberries (FDC ID: 1102710), Raisins (FDC ID: 1102640), Figs (NDB# 9089 and FDC ID: 1102632), Apricots (FDC ID: 1102625), Prunes (FDC ID: 1102639), Hazelnuts (FDC ID: 1100524), Walnuts (NDB# 12155), Sesame seeds (FDC ID: 1100608), Pumpkin seeds (FDC ID: 1100603), Soy milk (FDC ID: 1097542), Tofu (NDB# 16427), Tahini (FDC ID: 1100609); **: Fortified; §bioavailability of heme iron is 23%, and 3% of non-heme iron present in specific food

binding to ferroportin, a protein in many cell membranes, authenticating the exporter of the Fe from the cells. Systematic Fe metabolism is controlled at two levels: Fe absorbance from the diet and Fe recycling through macrophages. The effect of ferroportin inhibition by hepcidin is to

block the uptake of dietary Fe from the intestine and increase the accumulation of Fe in macrophages.[60] With sufficient iron stored in the body, hepcidin's concentration is high, and Fe absorption is suppressed. However, hepcidin is upregulated by many factors in all inflammatory conditions and hypoxia, resulting in anemia of chronic disease or inflammation.[61, 62] As a direct mediator of Fe homeostasis, reducing both intestinal Fe absorption and releasing Fe from macrophages for erythrocyte synthesis. Currently, hepcidin studies are limited by the availability of a suitable clinical assay.[63] Chronic, low-grade inflammation, characteristic of obesity,[64, 65] also a well-known risk factor for CRC (Table 1), triggers hepcidin production,[66] and is implicated in CRC tumorigenesis.[67] In inflammation, interleukin-6 (IL-6) is the primary inducer of hepcidin.[68] Regardless of the cause, every overexpression of hepcidin in blood results in more dietary Fe iron in the lumen and can have a prooncogenic effect. Cancer cells modulate Fe uptake and utilization through several mechanisms, first through local ferritin secretion and action on hepcidin[35] produced by cancer cells.[68] A higher hepcidin concentration in blood was found in CRC patients compared with healthy counterparts, which correlates with higher Fe accumulation in the colon tissue.[69] While hepcidin is a target for a potential therapeutic impact,[70] a recent study found that the response to Fe loading or depletion is specific to the CRC cell lines.[71] This study analyzed the growth of four human CRC cell lines in response to either increased concentrations or depletion of Fe.[71] Acute iron load had an inhibitory effect only on one cell line (HCT-116), while Fe depletion induced the complete growth arrest and detachment in three out of four cell lines (HT-29, HCT-116, SW-480).[71] Interestingly, after treatment with hepcidin, the growth of CRC cells starved of Fe was stimulated only in one cell line (HT-29).[71] Better and rationally informed therapeutics and understanding the mechanisms underlying hepcidin upregulation could be the first step toward developing drugs that, with other treatments, repress hepcidin and speed patient recovery.[60] Overproduction of hepcidin by IL-6 signalling is a significant factor that leads to functionally Fe-deficient cancer-related anemia. Inhibition of the IL-6 signalling pathway resulted in significant recovery of Fe-deficiency anemia. Also, IL-6 signalling might be one possible target pathway to treat cancer-related anemia disorders.[72] Daleptin (Fragmin), a low molecular weight heparin, has anti-inflammatory and antitumor effects besides its anti-coagulant effects. Heparin suppresses in vitro and in vivo hepcidin expression and reduces pro-inflammatory cytokines (IL-6 induces hepcidin synthesis, and heparin can suppress IL-6 concentrations in inflammatory conditions, decreasing the elevated hepcidin). During inflammation, an increase in local and/or systematic hepcidin results in iron overloading. Hepcidin can act as a double-edged sword by reducing intercellular space to combat inflammation.[73] Elevated hepcidin concentrations may help predict response to oral Fe supplementation. However, measuring hepcidin concentration is still not routinely or widely used in clinical practice.[74]

As for dietary Fe, the evidence regarding the role of Fe homeostasis in the body on the risk and progression of CRC is inconsistent. Research conducted under the Basque Screening Program found that elevated serum Fe, transferrin saturation, and ferritin were associated with an increased risk of CRC, especially in men.[75] Patients with advanced-stage CRC have significantly altered Fe homeostasis manifested as either Fe deficiency or depleted Fe stores.[69, 76] The negative correlation between Fe stores (observed as ferritin) and CRC was noted in two studies.[31, 77] Cross et al.[77] found an inverse association between Total Iron Binding Capacity (TIBC) and Unsaturated Iron Binding Capacity (UIBC) (indicators of low Fe stores) and colorectal adenoma, suggesting that low Fe stores act protectively. In the AMORIS study, TIBC showed a positive correlation with the risk for CRC.[78] The relationship between serum Fe and total cancer risk was described with a J-shaped curve by Wen et al.,[79] showing a significant increase in cancer risk. In a cohort study in Taiwan, an

increased risk for all cancers and mortality was observed in 25 and 35%, respectively, by increased Fe concentration in serum (≥ 120 µg/dL op. a. > 21.5 µmol/L).[79] Additionally, the risk of CRC is increased, if serum Fe concentrations are < 60 µg/dL op.a. < 10.7 µmol/L (males and females) and > 80 µg/dL op.a. >14.33 µmol/L (only females).[79] On the other hand, the European Prospective Investigation into Cancer and Nutrition (EPIC) Heidelberg Cohort found no association between Fe status in the body and the risk for CRC.[80]

The Interplay between Dietary Iron and Vitamin B12 in CRC

Despite the recognized role of nutrition in the context of the risk and progression of CRC,[32] especially about Fe, the results are mainly contradictory. One of the possible explanations is that all cohort studies examining the role of diet on cancer risk, progression, and survival (European EPIC and in the United States) accounted for the total dietary intake of Fe, along with the contribution from heme and non-heme Fe. Given the complexity of interactions between the body's stores and metabolism of Fe and its dietary sources, the bioavailability of Fe might provide clues on what happens with oncogenic processes in CRC.

Iron, especially highly bioavailable Fe, shares dietary sources with vitamin B12, one of the proposed cytoprotectors.[81] Foods of animal origin, especially milk and dairy products, are the only natural source of vitamin B12.[10] Due to its importance in complex C1 metabolic pathways,[82] vitamin B12, similar to folic acid, is considered to have positive alterations on cancers dependent on the C-1 metabolism disturbances, like CRC.[83, 84] Vitamin B12 plasma concentration was not found to be a significant factor in terms of CRC risk in the EPIC study[85] or the U.S. cohort study.[86] In contrast, the study conducted in Sweden found an inverse correlation with CRC.[87] Meta-analysis performed in 2016 did not find vitamin B12 to be significantly correlated with the risk for CRC.[88]

For optimal absorption, vitamin B12 too requires regular gastric activity, i.e., production of gastric pepsin and acid, and involves three proteins that, in a cascade-like process, bind vitamin B12: haptocorrin, intrinsic factor, and transcobalamin.[82, 89] For CRC, it is essential to emphasize that milk and dairy, besides being the source of vitamin B12 of the highest bioavailability,[10] contain the previously mentioned Ca.

To provide evidence favoring bioavailable Fe's role in CRC risk and prognosis, the case of Croatia, where several preliminary findings back up this hypothesis, will be presented. Croatia's early screening program in CRC detection has underperformed, like in many other European countries.[5] The high prevalence of overweight and obesity among adults is not characteristic of Croatia only.[90] The critical aspect is a diverse diet across Croatian regions, from Hungarian-Turkish-like in the eastern regions, Austrian-like in the northern parts, to the Mediterranean type in the coastal regions. Culinary diversity is not solely restricted to Croatia and can be seen in many countries worldwide.[91, 92] Regional differences become even more emphasized once CRC incidence and mortality rates between regions are compared.[93]

Traditionally, the diet in continental (Eastern) Croatia is abundant with processed and red meat, saturated fats, and spicy food; therefore, it can be characterized as a high-risk diet for CRC.[93] On the other hand, the diet in the coastal region can be seen as the Mediterranean diet or the CRC low-risk diet because of the well-proven beneficial effects on the CRC risk.[94] Considering that nutrition has the most substantial impact on CRC risk,[23, 32] one would expect higher incidence rates in continental Croatia. However, according to the latest incidence rates per 100,000 population from 2019, for C18 diagnosis (colon cancer excluding rectum), incidences are 43.3 in Osijek-Baranja County (Eastern Croatia), vs. 58.2 in Istria, 60.0 in Zadar and 69.9 in Split-Dalmatia County (coastal regions).[95]

Preliminary results support the hypothesis of a protective vitamin B12 role in CRC, mainly from milk and dairy products.

For a population with a high-risk diet, consuming vitamin B12 from milk, dairy products,

and fish represents independent protective factors for the population at risk due to their traditional dietary pattern.[93] Interactions between Fe and vitamin B12, i.e., a specific combination of foods of animal origin, seem to be a plausible explanation for those findings.[10]

Sun et al.[88] confirmed the protective effect of dietary vitamin B12 on CRC; with every additional 4.5 µg/day of dietary vitamin B12, the risk of CRC is reduced by 8.6%. Interestingly, authors[88] found the dose-response beneficial effect of vitamin B12. For comparison purposes, the recommended daily intake of vitamin B12 for adults (≥ 18 years), both genders, is 4.0 µg/day.[96]

Aspects of the Physiology of Digestion of Iron and CRC

Some aspects of the physiology of digestion may also modulate the effect of Fe on CRC. Prolonged exposure of the colorectum (the so-called luminal exposure) to excess amounts of Fe present in the feces increases the risk of CRC via enhanced colonocyte proliferation.[68, 97-99] For the potentially detrimental effect of Fe in the feces, pH is critical. Both colonic transit time and the composition of feces affect the pH in the large bowel.[10]

Although most dietary Fe (up to 80%) ends up in the feces, its composition is relatively stable; 25% consists of bacterial mass, 15% inorganic material, 5% fat, and (crude) dietary fiber. The amount of Fe in the faeces strongly correlates with phytic acid (e.g., whole grains contain large amounts of phytic acid).[100] Nevertheless, the amount of Fe in the faeces is 10 times higher than in most tissues.[10] Colon transit time is slightly shorter in men than women except in the rectosigmoid colon, regardless of age.[10] Lower faeces pH is considered protective in people with an increased risk for polyps and CRC adenomas.[101] Somewhat lower average pH is in the right (6.07 ± 0.38; proper CRC is more common in women) than in the left colon (6.84 ± 0.51; left CRC is more common in men).[10]

Diet as a Predictor of CRC Risk

Despite all the knowledge on the role of diet (and lifestyle) in CRC risk, which is constantly growing, diet has only been sporadically observed as a predictive factor in CRC pathology. An umbrella review of meta-analysis from 2021 found that higher intakes of dietary fiber, dietary calcium, yogurt, and lower alcohol and red meat consumption act protectively regarding CRC risk.[102] Yet, another analysis of the EPIC study data,[103] which included testing multiplicative gene-nutrient interactions, is inconsistent with the umbrella review. The corresponding association was found for alcohol, calcium, and dairy products, but their results also suggest that a lower CRC risk corresponds to higher dietary intakes of phosphorus, magnesium, potassium, riboflavin, beta carotene, and total protein.[103] A recent study analyzing the data from two cohort studies in China, outlines the importance of regionally-specific foods.[104] They analyzed adherence to the diet of 60, 161 men and 72,445 women aged 40–74, with the Chinese Food Pagoda (CHFP), a modified version of the Alternative Healthy Eating Index (AHEI-2010), and the Dietary Approaches to Stop Hypertension (DASH) in association with CRC risk. The inverse association with CRC risk was found only for the CHFP score.[104]

These mixed findings explain why diet is not the 'ideal' candidate for predictive models. Culinary diversity reflected through regional and country-specific dietary habits is just one part of the picture. Besides, in various parts of the world, some food groups include a variety of foods not available elsewhere, like dairy.

Successful use of diet (and lifestyle) as predictive factors is evident in models for the prediction of disease-free survival and overall survival in stage III CRC patients.[105, 106]

So far, the only model that seems right is the LiFeCRC score.[107] This is a lifestyle-based CRC risk prediction algorithm developed on the data from 255,482 participating in the EPIC study. The model included age, waist circumference, height, smoking, alcohol consumption, physical activity, vegetables, dairy products, processed meat, sugar, and confectionery. The risk score was found to be robust in terms of sex, especially

in individuals below 45 years. It accurately identified the risk for incident CRC in European populations.[107]

Considering everything said, the predictive model should focus on specific nutrients rather than foods. Nutrients selected for the prediction model should have a prominent role in the pathology of CRC, and Fe is undoubtedly a key player. Still, nutrient interactions need not be forgotten, for some may alter Fe profoundly. These interactions are integrated into the bioavailability calculations. In addition, by including biomarkers indicative of Fe homeostasis in the body, namely hepcidin, the model could serve as a valuable tool for CRC risk and recurrence assessment.

Conclusion

So far, prevention programs in European countries have not yielded significant improvements in the early detection and diagnosis of CRC. While the number of patients continues to rise, the importance of diet and lifestyle habits as a cornerstone for CRC prevention has not been adequately emphasized through public health campaigns. The intricate interactions between diet and the human body and their role in the pathology of CRC remain a subject of ongoing debate within the scientific community. Observational studies, while valuable, often lack the statistical power to provide definitive evidence. However, the role of iron (Fe) in CRC is particularly noteworthy, not only for its potential in CRC prevention but also for its relevance in prognosis and individualized therapy.

Hepcidin, a pivotal protein in iron homeostasis, has shown promise in research but remains underexplored as a potent prognostic and diagnostic marker in clinical practice. Moreover, hepcidin represents an intriguing therapeutic target that warrants further investigation. Indeed, many countries can relate to the culinary diversity mirrored in the CRC incidence observed in Croatia. Although limited in scope, preliminary results have raised several questions regarding the role of dietary sources of iron, its bioavailability, and its impact on the bodily homeostasis of CRC.

Clarifying the significance of iron bioavailability and unveiling the prognostic potential of hepcidin could prove invaluable and influential in developing predictive models for CRC risk and recurrence.

Conflict of Interest

None declared.

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