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Folate in colorectal cancer: beneficial or detrimental?

Kolorektal kanserde folat: yararlı mı, zararlı mı?

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Abstract

Folate is a water-soluble B-group vitamin found in various foods including green leafy vegetables, hens' eggs, and legumes. Folate has an essential role in DNA repair, methylation, and synthesis. Folate deficiency causes neural tube defects, megaloblastic anemia, cardiovascular diseases, and cancer. Foods are enriched with folic acid, a synthetic monoglutamate form of folate, and folic acid supplementation is provided in many countries because the increased need for folate during pregnancy cannot be met only with food. Due to the important roles of folate in DNA synthesis, there are concerns that exposure to high doses of folic acid may cause colorectal cancer. Studies support that folic acid taken before polyp development has protective effects from colorectal cancer. On the other hand, folic acid supplementation induces colorectal cancer after polyp formation. It is also thought that epigenetic modifications affecting folate metabolism play a role in this process. In conclusion, folate intake at optimal levels and appropriate timing may exert protective effects against colorectal cancer, whereas folic acid consumed in supraphysiological doses and at later stages may promote tumor progression and increase the likelihood of carcinogenic progression of premalignant lesions.

Özet

Folat yeşil yapraklı sebzeler, yumurta ve baklagiller gibi birçok besinde bulunan suda çözünen bir B grubu vitamini olarak kabul edilmektedir. DNA onarımı, metilasyonu ve sentezi gibi önemli rolleri bulunur. Eksikliğinde nöral tüp defekti, megaloblastik anemi, kardiyovasküler hastalıklar ve kanser gibi hastalıklar görülmektedir. Özellikle gebelik döneminde ihtiyacın artması ve bunun besinlerle sağlanamamasından ötürü birçok ülkede besinler folatın sentetik monoglutamat formu olan folik asitle zenginleştirilmektedir ve folik asit takviyesi sağlanmaktadır. DNA sentezindeki önemli rollerinden dolayı yüksek doz folik asite maruziyetin kolorektal kansere neden olabileceğine dair endişeler de mevcuttur. Yapılan araştırmalar polip oluşumundan önce alınan folik asidin kolorektal kanserden koruyucu etkileri olduğunu desteklemekte ancak polip oluşumundan sonra kolorektal kanser gelişimini indüklediğini ortaya koymaktadır. Ayrıca folat metabolizmasını etkileyen epigenetik modifikasyonların da bu süreçte etkili olduğu düşünülmektedir. Sonuç olarak, optimal düzeylerde ve doğru zamanda alınan folat, kolorektal kanser riskini azaltıcı etkilere sahipken; fizyolojik sınırların üzerinde ve geç dönemde alınan folik asit, tümör progresyonunu destekleyebilir ve premalign lezyonların kansere dönüşme riskini artırabilir.

Introduction

First isolated from spinach in 1941, folate is a vitamin derived from the Latin word folium, meaning leaf (1). Once the effectiveness of folic acid in preventing neural tube defects was understood, food was fortified with folic acid in many countries, and folic acid supplements were given to pregnant women. Given this, the role of folate in causing colorectal cancer (CRC) has always been controversial. Although treatment methods are advancing, CRC still causes approximately 900,000 deaths annually and accounts for 10% of cancer-related deaths (2). According to the Turkish Cancer Statistics published by the Ministry of Health in 2025, CRC was the third most common type of cancer in women and men in our country in 2020 (3). It is important to point out that this illness is generally characterized by its occurrence in individuals over the age of 50. However, its incidence among younger people has also started to increase (4). Studies show that only a small percentage of CRC cases are hereditary. Additionally, research demonstrating a rapid increase in incidence among migrating to Western-style countries highlights the significant role of environmental factors in CRC development (5, 6). Diet, lifestyle, and even the location of the existing lesion can influence the risk of CRC development (7, 8). The potential impact of current folic acid supplementation programs on CRC development, whether positive or negative, should not be overlooked. Especially, the relationship between folate metabolism, cell growth, and nucleic acid synthesis is an important indicator that even a minor effect could lead to DNA damage. Additionally, folate influences epigenetic mechanisms by playing a key role in the methylation process. In folate deficiency, imbalances in homocysteine metabolism disrupt both the *de novo* biosynthesis of purine and thymidylate, as well as the formation of S-adenosylmethionine (SAM) (9). Excessive folic acid intake or accumulation of unmetabolized folic acid in circulation due to deficiency of dihydrofolate reductase (DHFR) enzyme, imbalances in folate metabolism may adversely affect both nucleotide synthesis and methylation processes. In particular, disruptions in *de novo* biosynthesis of purines and thymidylates may impair DNA replication and repair (10). Furthermore, reduced SAM production may lead to deficiencies in epigenetic regulatory processes such as DNA, RNA and histone methylation, resulting in hypomethylation or targeted hypermethylation and silencing of tumor suppressor genes. These epigenetic alterations play an important role in CRC, especially in the initial stage. In addition, impaired purine metabolism can promote cell proliferation, invasion and development of therapeutic resistance by activating tumor-associated signaling pathways such as mTOR and Notch-1. Thus, both folate deficiency and folic acid exposure above physiological limits may contribute to the process of colorectal carcinogenesis by threatening genomic stability through SAM levels, purine and thymidylate synthesis (10-12). Therefore, this review aims to assess the effect of folate on CRC and examine its potential mechanisms.

Folate, Folic Acid

Folate (vitamin $B_{9)}$ is an important member of the water-soluble B vitamin family. This, composed of a pteridine ring linked to p-aminobenzoic acid and one or more glutamate residues, is called pteroylglutamic acid (13, 14). Folic acid is the synthetic monoglutamate form of folate found in dietary supplements and enriched foods (15). Folic acid is significantly superior to folate in terms of bioavailability and stability because it is in oxidized form and contains only one conjugated glutamate residue (16, 17). The reason is that due to storage and preparation conditions, the bioavailability of folate found in foods decreases by approximately 50% (15). Folate, as a coenzyme in one-carbon transfer and processing reactions, plays a key role in nucleotide synthesis, DNA repair, methylation, gene expression regulation (18, 19), cell division, and tissue differentiation (20). Information about the mechanisms regulating body folate balance is still quite limited (21). Dietary folate is in the form of polyglutamate and cannot cross the cell membrane of the small intestinal epithelium. It must therefore be hydrolyzed to monoglutamate form. Folic acid diffuses since it is in the monoglutamate form (22-24).

Homocysteine methionine synthase, for which vitamin B12 is a coenzyme, is responsible for methionine synthesis in folic acid metabolism (22). The methionine synthase reaction is important because it allows the regeneration of tetrahydrofolate (THF), which is necessary for the formation of 5,10-methylenetetrahydrofolate (MTHF) and 10-formyl-THF, which are used in the synthesis of thymidylate and purine, respectively (25). The proper functioning of these pathways is vital, as disruptions in thymidylate and purine synthesis can lead to impaired DNA replication, genomic instability, and increased susceptibility to tumorigenesis (10).

Since it cannot be synthesized in the human body, folate is an essential vitamin and must be obtained from natural sources such as green leafy vegetables, eggs, asparagus, broccoli, brussels sprouts, whole meal cereals, pseudocereals, yeast, organ meats, pulses such as green and dried lentils, peanuts and citrus fruits (26, 27). In addition to dietary sources, many bacteria in the gastrointestinal tract, such as *Bifidobacterium adolescentis*, are capable of synthesizing folate at a rate close to that ingested through food (26-28) . However, the absorption rate and bioavailability of the synthesized amounts are not yet fully known. According to the Turkey Dietary Guidelines (TÜBER), the daily folate requirement for children aged 2-9 years is 120-200 μg, for adolescents aged 10-18 years it is 200-330 μg, for adults over 18 years it is 330 μg, for pregnant women it is 600 μg, and for lactating women it is 500 μg (27).

Colorectal Cancer Incidence, Risk Factors and Screening

The Western type of diet has been identified as a contributing factor to the increasing incidence and mortality of CRC in low- and middle-income countries, while in high-income countries, the incidence and mortality pattern are either decreasing or stabilizing (29). However, it has also been reported that the incidence of CRC in individuals younger than 50 years of age is increasing in high-income countries (30). A substantial body of epidemiological studies reveals a strong association of CRC with male gender and increasing age (2, 31, 32). Although CRC is generally asymptomatic until it reaches advanced stages, metastasis is observed in approximately 20% of diagnosed individuals (2, 33). Consequently, the significance of periodic screening for the early diagnosis of the condition is underscored. The American Cancer Society (ACS) recommends that healthy individuals with an average risk of CRC and a life expectancy of more than 10 years begin regular screening at age 45 using high-sensitivity stool-based tests, colonoscopy, or other visual examination methods. For individuals aged 50 and older, screening is strongly recommended (8).

The Role of Nutrition in Colorectal Cancer

1. Lifestyle and Dietary Factors in Colorectal Cancer

Environmental factors such as obesity and obesity-related insulin resistance, inadequate physical activity, unbalanced nutrition, microbiota profile, and high smoking and alcohol consumption are important in the development of CRC (4). While the Western dietary pattern increases the risk of CRC, the Mediterranean diet, semi-vegetarian diet, and pescetarian diet have been associated with a reduced risk. These dietary patterns are rich in dietary fiber, polyphenols, anti-inflammatory and antioxidant components, which are thought to beneficially modulate the gut microbiota, reduce oxidative stress, and suppress biological pathways involved in tumor development (34). A diet comprising milk, fiber, vegetables, fruits, and whole grains has been shown to reduce the risk of developing CRC (32, 35). High consumption of refined carbohydrates added sugars, fats, alcoholic beverages, and red or processed meat increases the risk of CRC development (6, 7) (Figure 1). It is acknowledged that vitamins and minerals, including folate, vitamin D, vitamin E, vitamin B6, calcium, selenium, magnesium and iron, have been demonstrated to influence ATP production and cell metabolism. Consequently, these nutrients may also be implicated in the development of CRC (32, 36).

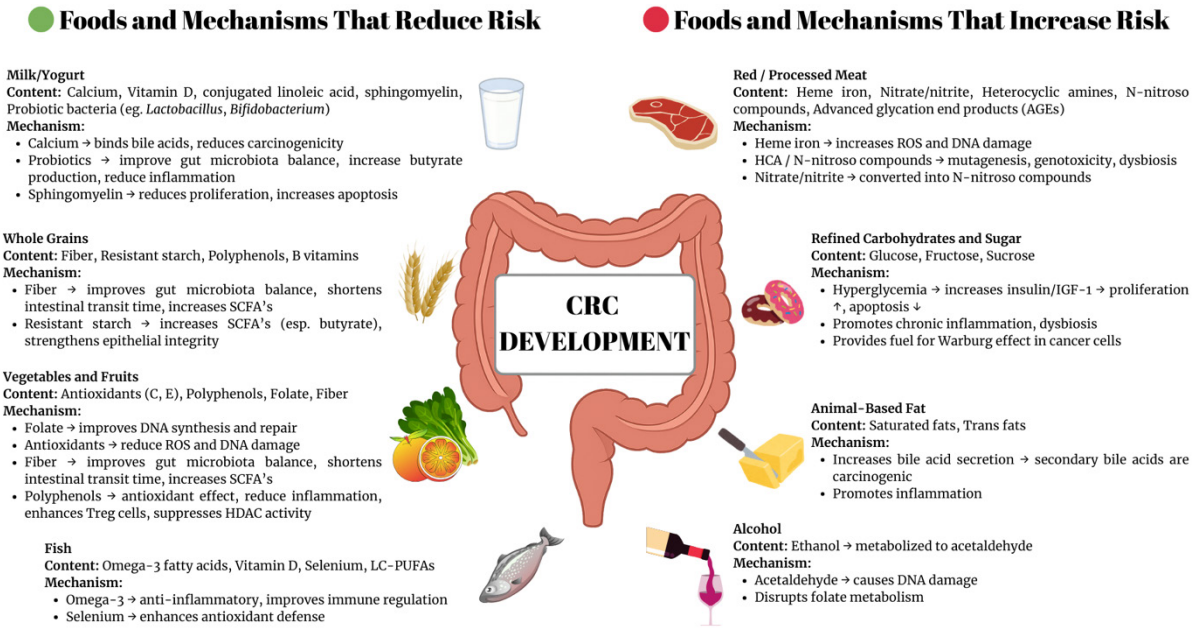

Figure 1. Dietary components and their mechanisms in CRC development. Foods such as milk/yoğurt (dairy products), whole grains and resistans startch complex, vegetables, fruits, and fish (and their contents) support anti-inflammatory, antioxidant, and pro-apoptotic pathways, thereby reducing CRC risk. Conversely, red/processed meat, refined carbohydrates, animal-based fat, and alcohol contribute to CRC risk through mechanisms including DNA damage, chronic inflammation, insulin/IGF-1 signaling, and dysbiosis. CRC; colorectal cancer, HDAC; histone deacetylase, SCFAs; short-chain fatty acids, ROS; reactive oxygen species, HCA; heterocyclic amines, LC-PUFAs; long-chain polyunsaturated fatty acids.

Nutritional support plays a crucial role in the treatment of CRC. The Spanish Society of Medical Oncology (SEOM) and the European Society for Clinical Nutrition and Metabolism (ESPEN) recommend that cancer patients receive 25–30 kcal/kg of energy per day, similar to healthy individuals; therefore, energy restriction should be strictly avoided (37, 38). For protein intake, ESPEN recommends 1–1.5 g/kg/day, while SEOM suggests 1.2–1.5 g/kg/day (38). Colorectal cancer patients are at high risk of developing nutrient deficiencies due to reduced food intake, impaired digestion and absorption, and a predisposition to a catabolic state (39). Various side effects

may arise due CRC itself and its treatment. Gastrointestinal disturbances frequently occur in patients receiving radiotherapy to the pelvic region, including radiation enteritis, mucosal atrophy, progressive fibrosis of the intestinal wall, and chronic diarrhea. Even before these adverse effects emerge, it is beneficial to adopt a diet consisting of easily digestible foods, while excluding hard-to-digest fatty meals, raw milk, raw fruits and vegetables, carbonated beverages, fruit juices, and spices (38, 39). Chemotherapy may lead to a wide range of adverse effects, including taste disorders, loss of appetite, diarrhea, constipation, mucositis, fatigue, esophagitis, nausea, aversion to food, vomiting, neutropenia, hypertension, bleeding, allergic reactions, weight loss, dry mouth, psychological distress, electrolyte imbalances, and dehydration (40). Managing these effects requires tailored nutritional strategies; for instance, patients with nausea may benefit from consuming bland, stomach-friendly options like bananas, rice, or lightly toasted bread with lemon, while those with reduced appetite are encouraged to consume small, frequent, and calorie-dense meals. Additionally, it is recommended that all CRC patients eliminate overly salty, pickled, smoked, fried foods, and alcohol from their diets (39, 41).

A diet consisting of healthy nutrition has been shown to not only prevent the development of CRC but also reduce mortality in those who contract the disease. A multicenter study showed that stage III colon cancer patients who ate a healthy diet, engaged in regular physical activity and had a normal body mass index (BMI) had a 42% lower risk of death than those without a similar lifestyle. However, the nutritional approach should be tailored to the specific needs of each patient, contingent on their prognosis and treatment regimen. (42).

2. Gut Microbiota

In addition to hereditary factors, environmental conditions influence both the immune system and the microbiota, contributing to population-level variations in CRC risk. Given their direct interaction with the gastrointestinal tract, diet and microbiota are particularly effective in the prevention and treatment of gastric and CRCs compared to other malignancies (43, 44). The microbiome has also been demonstrated to influence the development and progression of CRC, as well as the patient's response to various systemic treatments (6). Diet has a dominant effect on both the microbiota and the host immune response. Poor dietary habits have the potential to cause dysbiosis, leading to the production of harmful metabolites and genotoxins. These, in turn, can promote inflammation and ultimately contribute to the development of cancer (45, 46). The certain gut microbiota is reported to contribute to the development of CRC by producing folate and biotin, which plays a role in regulating epithelial proliferation. While in a balanced microbiota this production contributes to epithelial homeostasis, in dysbiosis these metabolites may promote uncontrolled proliferation and contribute to CRC pathogenesis (6).

Relationship Between Colorectal Cancer and Folate

1. Protective Effects of Folate

In cancerous cells, DNA replication and cell division occur irregularly and rapidly (22). Antifolate chemotherapy agents, such as methotrexate and 5-fluorouracil (5-FU), inhibit DNA synthesis and inhibit tumor growth by reducing the proliferation of neoplastic cells. Paradoxically, the results of epidemiological studies have shown that the incidence of CRC decreases as the consumption of folate-containing foods increases (47, 48). The role of folate in the development of CRC is controversial: This vitamin is thought to be protective in the early stages of carcinogenesis but may accelerate the growth of premalignant lesions or micrometastasis. Folate plays an essential role in DNA synthesis, methylation, and one-carbon metabolism. Adequate folate intake is necessary for the proper functioning of these processes, particularly for maintaining genomic stability and supporting normal cell division. However, the same mechanisms that processfolate protective can paradoxically accelerate tumor development in the presence of premalignant

lesions. Increased DNA synthesis may lead to enhanced cell proliferation, while alterations in the methylation cycle can affect gene expression through epigenetic mechanisms. Therefore, in individuals with pre-neoplastic changes, high folate intake may promote tumor progression. The relationship between circulating folate and folic acid concentrations measured at the time of diagnosis and mortality and morbidity is unknown (49). Another reason for the inconsistent findings regarding the association between folate and folic acid and CRC is the differences in study design. Methodological discrepancies between observational and interventional studies lead to contradictory results. Numerous large-scale international studies have demonstrated that increased intake of folate/folic acid is associated with a reduced risk of CRC (50-52). In a meta-analysis that included 27 studies examining the relationship between folate intake and CRC incidence, it was concluded that there was an inverse relationship between CRC incidence and folate intake (23). A systematic review and meta-analysis published in 2023, which included prospective studies, demonstrated that high folate intake reduces the risk of CRC in populations in the Americas and Europe. Moreover, the study established that increasing folate intake in individuals who consumed moderate to high amounts of alcohol resulted in a reduced risk of CRC. This effect was not observed in individuals who did not consume alcohol (48). This may be explained by the fact that alcohol consumption negatively affects folate absorption in the gastrointestinal tract and its intracellular metabolism, leading to folate deficiency. This condition impairs DNA synthesis and methylation processes, particularly in rapidly dividing cells. In response to folate deficiency, cells increase the expression of folate transporter proteins and activate regulatory mechanisms to support intracellular folate accumulation (9). In Türkiye, a clinical study investigating the association between serum folic acid levels and CRC was conducted with 60 patients. In this study, serum cobalamin and folate levels were measured as markers of liver metastasis in stomach and colon cancer. The results of this study showed that plasma folic acid levels were found to be low in both cancer groups (53). International studies examining the blood levels of folate and folic acid and the development of colorectal cancer have also yielded conflicting results (54-56). In a prospective study involving 2024 CRC patients with stages I-III within the FOCUS international consortium, the relationship between blood folate, folic acid and folate catabolism product concentrations at the time of diagnosis and survival and later recurrence was investigated. The findings of the study indicated an absence of a significant relationship between circulating folate, folic acid and folate catabolites and survival. Despite the absence of any established correlation between folate and its catabolites and cancer recurrence, it has been observed that elevated levels of folic acid in circulation are directly associated with an increased risk of recurrence. However, dietary sources of folate catabolites are not associated with CRC recurrence or overall survival (49). According to the data from the Turkey Nutrition and Health Study published in 2019, folate intake is sufficient for both men and women in our country. However, 34.4% of individuals over the age of 15 consume less than the recommended amount of folate (57). To the best of our knowledge, no study has currently been conducted in our country that examines the risk of CRC in about folate intake. Therefore, further studies should better show the potential risks that may cause from folate deficiency.

2. Potential Risks of Excessive-Dose Folic Acid

After it was understood in 1991 that approximately 8 out of 10 neural tube defect (NTD) cases were caused by folate deficiency, folic acid supplementation began to be included in the public health policies of some countries (58). However, this intervention has also prompted concerns about the potential risks linked to excessive folic acid intake. The Aspirin/ Folate Polyp Prevention Trial is an investigative study that randomly assigned participants with a recent history of colorectal adenoma to receive either 1 mg of folic acid or a placebo supplement daily for a period of 3–5 years. The study's findings indicated an elevated risk of advanced multiple colorectal adenomas in the folic acid

supplement group (49). A second extended follow-up study was conducted as a continuation of this study and concluded that folic acid causes an increase in the risk of sessile polyp formation in individuals who have completed cancer treatment (52, 59) . While some countries around the world fortify flour with folic acid to prevent NTDs, others choose not to do so due to concerns about the potential risks associated with high folic acid intake (60). Theoretically, folic acid competes with 5-MTHF, the main form of folate in the blood, potentially interfering with natural folate metabolism, transport, and regulatory functions (22).

Excessive folic acid intake may drive CRC development through multiple molecular mechanisms. The relationship between folic acid exposure and CRC risk is thought to follow a dose- and time-dependent "U"- or inverted "J"-shaped curve (60). Folate serves as a central component in nucleotide synthesis and methyl group donation, ensuring genomic stability through the production of thymidylate via 5,10-methylenetetrahydrofolate, and regulating epigenetic modifications through SAM-dependent methylation. However, when folic acid intake exceeds physiological thresholds of 200-266 μg the low activity of human DHFR becomes insufficient for its complete metabolism, resulting in the accumulation of unmetabolized folic acid in the circulation (62, 63). This may lead to aberrant DNA methylation patterns, promote tumor progression via SAM-mediated hypermethylation of tumor suppressor genes, and enhance cellular proliferation due to increased nucleotide. High folate exposure, especially after the formation of dysplastic lesions, may further stimulate the growth and invasiveness of them. These effects are associated with the activation of oncogenic pathways such as Notch-1 and Wnt/β-catenin and may induced in tumors that overexpress folate receptor alpha (FOLR1), a feature frequently observed in CMS2 subtypes of CRC (64, 65). Also, there is evidence that exposure to 0.5-1 mg of folic acid over an extended period can result in neurological damage in individuals with vitamin B12 deficiency (65).

Proinflammatory cytokines regulate essential cellular processes such as differentiation, proliferation, migration, and apoptosis. In CRC, cytokines such as IL-1β, IL-6, TNF-α, and IL-12 have been reported to increase significantly from the early stages of the disease. IL-1β may provide prognostic information in early stages; however, its levels tend to decrease in advanced stages, limiting its prognostic utility in those cases. TNF-α, on the other hand, maintains relatively stable levels across all stages, making it useful primarily for diagnostic purposes (66). Additionally, cytokines of the IL-12 family play a critical role in regulating both innate and adaptive immune responses and are involved in shaping the tumor immune microenvironment (67). In this context, the increase in circulating proinflammatory cytokines triggered by unmetabolized folic acid observed following folic acid supplementation and their known association with CRC underscore a potentially important mechanistic link. This is especially relevant when evaluating the possible cancer-promoting effects of folic acid supplementation. A study conducted in the United States also found that children had high blood folate concentrations (68). Similarly, in a study conducted in Brazil, one of the countries that implemented a policy of fortifying foods with folic acid, unmetabolized folic acid was found in the blood of 80% of the participants. The study revealed that unmetabolized folic acid led to an increase in proinflammatory cytokines (TNF-α, IL-1β and IL-12) in the blood (62). Studies in the American and Canadian populations reported a striking increase in plasma folic acid levels in adults after the introduction of folic acid fortification of foods (68, 69). Furthermore, during this period, a concurrent increase in the incidence of CRC was observed in the populations of both countries. Although these observations are consistent with the results of animal experiments and clinical studies, they do not prove that folic acid supplementation alone increases the risk of CRC (19). In response to the claims made on this issue, the hypothesis advanced was that folic acid supplementation did not affect the increase in CRC cases observed in the United States towards the end of the 1990s. This is likely due to the very short interval between the initiation

of folic acid supplementation and the observed increase in CRC incidence, which does not align with the expected latency period of cancer development. Arguments have been made that the supplements reduce the risk of CRC, with the decline in CRC incidence in subsequent years providing supporting evidence (4). Considering the numerous studies conducted on this subject, individuals must be mindful of the appropriate and safe intake amounts in order to reap the benefits of folic acid supplements while mitigating potential risks.

3. Genetic Modifications

Folic acid supplementation is considered appropriate in the treatment of individuals with the MTHFR 677 C>T gene polymorphism, which affects the MTHF-reductase enzyme, which plays an important role in folate metabolism (17, 70). A study investigating the interaction between genes associated with CRC risk and total folate intake evaluated 13,498 cases and concluded that CRC cases were mostly associated with male gender, higher BMI, and lower daily folate consumption. In this study, a significant association was identified between folate consumption-related CRC risk and glutathione S-transferase A1 (GSTA1), tonsuka-like DNA repair protein (TONSL) and aspartylglucosaminidase (AGA) genes (20). GSTA1 is involved in cellular detoxification through glutathione and may be indirectly influenced by folate levels via homocysteine metabolism (20, 71). Mutations in this enzyme impair the detoxification of carcinogens. The TONSL gene is part of a complex responsible for the repair of DNA double-strand breaks, and its mutations can increase DNA damage, thereby contributing to tumor development. AGA is involved in the lysosomal degradation of glycoproteins; an association between high folate intake and increased expression of this gene may influence CRC risk (20, 72). To date, no studies have reported a direct link between AGA and cancer (20).

4. Folic Acid Use in Colorectal Cancer Chemotherapy

Folate is an essential micronutrient required for DNA synthesis, cell division, and normal cellular development. Considering the biochemical role of folate, folate-dependent enzymes have become common targets for chemotherapeutic agents. Antifolate chemotherapy drugs, classified as antimetabolites, function by disrupting cellular metabolism to inhibit cell proliferation or induce apoptosis. These agents are structurally similar to folate and act by binding to or inhibiting intracellular folate enzymes. During antifolate therapy, determining the optimal dose and timing of folate supplementation is crucial to minimize treatment-related toxicity while maintaining therapeutic efficacy. However, there is limited information in the literature on this issue. Although variables such as the type of folate, timing, and dose must be carefully considered, it is often hypothesized that folate exposure may reduce the efficacy of antifolate therapies. On the other hand, it is important to note that antifolates are typically administered in doses (mg/m^2) far exceeding those of μg level of dietary or supplemental folate (73).

5-Fluorouracil, commonly used in CRC treatment, is a pyrimidine analog of uracil and thus functions as a pyrimidine antagonist. Increased intracellular folate levels enhance the cytotoxic efficacy of 5-FU. Therefore, it is frequently administered in combination with folinic acid (leucovorin). Standard chemotherapy protocols also combine 5-FU with systemic agents such as irinotecan and oxaliplatin; examples include FOLFOX, FOLFIRI, FOLFOXIRI, and CAPEOX regimens (74, 75).

Studies focusing on antifolate agents have shown that low folate status or insufficient folic acid intake is associated with an increased risk of toxicity. Conversely, studies evaluating fluoropyrimidine-based treatments have reported that higher folate levels and intake may also be linked to an elevated toxicity risk. These findings suggest that both insufficient and excessive folate intake may influence chemotherapy-related toxicities. Understanding how the relationship between folic acid and chemotherapy affects overall survival and progression-free survival is crucial. In this context, high-quality prospective cohort studies

are needed to investigate the role of circulating biomarkers and folate or folic acid intake in treatment-related toxicity and treatment efficacy outcomes (76).

In light of these findings, it becomes increasingly important to develop personalized dosing strategies in clinical practice, particularly for nutrients such as folate and folic acid that are known to potentially interact with chemotherapy regimens.

Although many studies evaluating the relationship between folate/folic acid intake and CRC have the advantages of large sample sizes and long-term follow-up, they also present several methodological limitations. In Türkiye, the number of studies on this topic is quite limited, leading to a lack of national-level data. In particular, the homogeneity of samples in some studies restricts the generalizability of results to different demographic groups. Moreover, the impact of folic acid supplementation or food fortification on plasma folate levels has not been sufficiently considered, and in some cases, the use of dietary supplements has been excluded from the analysis. While folate intake is generally assessed through dietary data, most studies do not include plasma folate measurements, which could more accurately reflect biological activity. Additionally, potential confounding factors such as genetic polymorphisms like MTHFR, as well as alcohol and multivitamin use, are often inadequately controlled. Some studies assess only the overall risk of CRC without examining differences across cancer stages. Furthermore, there is a lack of data regarding the interactions between folic acid supplementation and chemotherapeutic agents. Therefore, there is a clear need for large-scale, multicenter studies, particularly within Türkiye, that include diverse subgroups such as older populations and various ethnic groups.

Conclusions

In many countries, foods are fortified with various micronutrients, including folate, to prevent vitamin and mineral deficiencies. During pregnancy, dietary intake alone is insufficient to meet the increased folic acid requirements; therefore, folic acid supplementation programs are implemented for pregnant women as part of national health policies. However, for the general population outside of pregnancy, there is no universally recommended standard dose of folic acid. For this reason, individualized approaches should be adopted, considering factors such as genetic profile, serum folate levels, and medical history. In the prevention of CRC, uncertainties remain regarding the optimal dose, duration, and timing of folate supplementation. High-dose supplementation may disrupt folate metabolism and lead to an accumulation of unmetabolized folic acid in circulation. Moreover, the relationship between folate and folic acid levels at the time of diagnosis and CRC-related mortality and morbidity has not yet been fully clarified. Following CRC treatment, folic acid supplementation is not recommended due to the risk of recurrence. In contrast, there is no need to restrict folate intake from natural dietary sources. Further advanced studies are needed to elucidate the mechanisms by which folic acid influences CRC development and progression.

Author Contribution

Conceptualization: AA, HKA; Design: AA, HKA; Review: AA; Writing: AA; Editorial review & editing: HKA.

Conflict of Interest

The authors declare that they have no conflict of interest.

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