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Review

The relationship between folic acid and colorectal cancer; a literature review

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ABSTRACT

The objective: this study aims to investigate the relationship between folic acid and colorectal cancer (CRC).
Methods: google scholar, Pubmed, Pubmed central were searched from 1994 to 2022 for articles on the association between folic acid and CRC using the combinations: folic acid and colorectal cancer risk, folic acid and colorectal cancer survival, folic acid and colorectal cancer recurrence.
Main message: to describe and discuss the effect that folic acid might play on colorectal cancer (CRC) risk, recurrence and survivals, taking into account the possible differences between the men and women.
Conclusion: Our article supports the idea that says: vit-B9 has a dual-modulator effect on CRC carcinogenesis. However, its role in preventing recurrence and improving survival rates remains unresolved with a possible potential role of folate metabolism genotype variations. Therefore, more evidence from clinical studies is needed.

1. Introduction

CRC is one of the most threatening tumors, comprising 10.2% of all diagnosed tumors and 9.2% of cancer-related mortality worldwide [1]. In 2018, it was ranked the third malignancy in incidence, and the second malignancy in mortality related to cancer [2]. The CRC rates are expected to increase [2] despite the screening programs [3].

Vit-B9 (folic acid; FA) is a water-soluble vitamin that plays a significant role in de novo synthesis of purines and thymidine as well as its essential role in preventing several disorders such as megaloblastic anemia, atherosclerosis, neural tube defects and cancer [4]. Herein, we aim to clarify the relationship between folic acid and CRC.

2. Methods

Google scholar, Pubmed, Pubmed central were searched from 1994 to 2022 for articles on the association between folic acid and CRC using the combinations: folic acid and colorectal cancer risk, folic acid and colorectal cancer survival, folic acid and colorectal cancer recurrence.

3. Discussion

3.1. Folate & CRC risk: folic acid is a double-edged sword

The relationship between folate and cancer seems to be contradictory [4]. In malignant cells and other rapidly dividing ones, antifolate agents slower the tumor growth as they cause ineffective DNA synthesis [4]. However, folate deficiency predisposes normal tissues to malignant transformations; which explains the protective role of folate in preventing carcinogenesis [4]. However, Hubner, R A et al [5] study found a similar results, suggesting a dual-modulator effect (Fig. 1) of folate on the CRC tumorgenesis; in which folate has a preventive role in the absence of malignant foci and a provoking effect in the presence of such foci (Table 1).

The association between folate intake and CRC risk seems to be complicated as it depends on multiple factors such as gender, age, alcohol consumption, and smoking [6]. However, some studies found that low plasma folate was associated with lower CRC risk [7,8]. Whereas, other studies found no effect of folate on CRC risk at all [9–11]. In 2007, a randomized-control trail (RCT) was performed by Cole, Bernard F et al [12], found that 1 mg/dl intake of folic acid had no effect

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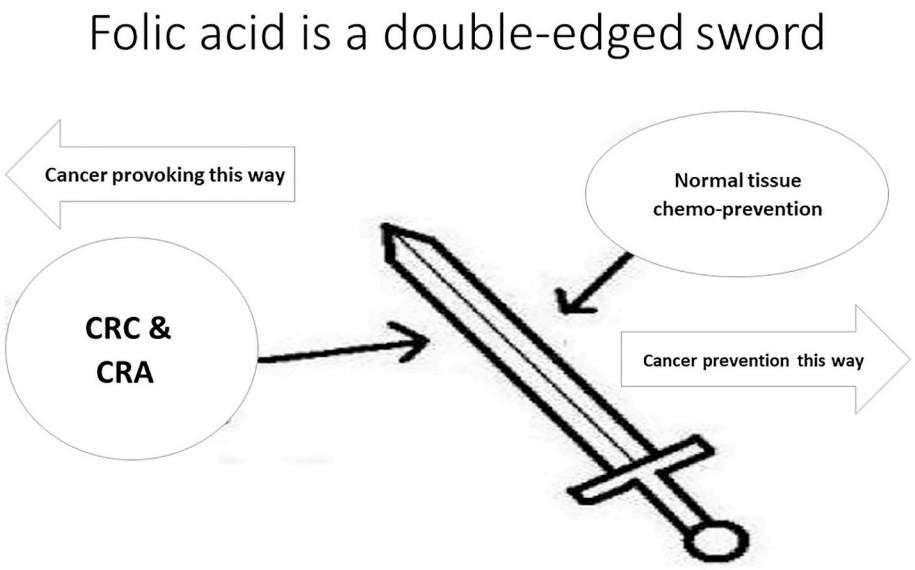

Fig. 1. Vit-B9 has a dual-modulator effect on CRC carcinogenesis.

Table 1
Folate & CRC risk.

Study (first author)	size	Duration	Study design	Effect on crc risk
VAN GUELPEN, B ET AL 2006 (7)	663	4.2 years	Prospective study based on the Northern Sweden Health and Disease Study (NSHDS)	Low folate status is associated with decreased CRC risk
COLE, BERNARD F ET AL 2007 (12)	1021	10 years	Randomized-control trial (RCT)	No effect
GAO, QIN-YAN ET AL 2013 (13)	800	3 years	RCT	Folate supplementation is associated with decreased CRC risk
GYLLING, BJÖRN ET AL 2014 (8)	993	10.8 years	Nested case-control study within NSHDS, included subjects from Västerbotten Intervention Program (VIP) & Mammography Screening Project (MSP) populations	Low folate status is associated with decreased CRC risk
QIN, TINGTING ET AL 2015 (10)	–	–	Meta-analysis	No effect
DING, HUI ET AL 2016 (29)	1310	participants without CRA was 2.1 years compared with 1.8 years for patients with CRA.	Prospective study	High folate status is associated with decreased CRC risk & recurrence
MOAZZEN, SARA ET AL 2018 (9)	–	–	Meta-analysis	No effect
MOAZZEN, SARA ET AL 2020 (11)	405	10 years	Case-control	No effect

on reducing CRC risk, in contrast with Gao, Qin-Yan et al [13], which revealed a significant reduction in colorectal adenoma especially left-sided ones. Furthermore, in Larsson, Susanna C et al [14] cohort study, caffeine and smoking were tested for their effect on the relationship between vit B9 and CRC. Interestingly, caffeine has not modified the relation, in contrast with smoking, which suggests that smokers may take advantage from high vit B9 intake. In 2013, a prospective study found that folate fortification may decrease the cancerous effect of alcohol on colorectal mucosa [15].

In 2011, a study performed by Sie KK, Medline A et al [16]determined that maternal folic acid supplementation recommended to women at child-bearing-age was associated with lower colorectal cancer risk in the offspring. However, in 2020, a case-control study found an opposite result [10]. Interestingly, the association between folate and CRC risk may differ between genders. This result was observed in a cohort study performed by Brink, Mirian et al [17]; which stated that no association was found between Dietary folate intake and colon cancer risk in both sexes, regardless of the presence of k-Ras mutations. However, this situation was different for rectal cancer, as an inverse association was found between folate intake and rectal cancer risk in men especially with K-Ras mutated tumors, whereas an increased association was found in women.

3.2. Folate & CRC survival

Several researches were concerned about the effect of folic acid on CRC survival rate with mixed results ranging from supporting to opposing its use in CRC patients. According to Ting PC, Lee WR [18] study; patients who take folic acid had a significant improve in CRC survival, that was attributed to its role in inhibiting colorectal cancer cell proliferation and migration. However, a different result was observed in Focus consortium [19] study as folic acid levels and its derivatives were not associated with neither CRC survival nor CRC recurrence. In 2003, a cohort study found that CRC patients who took both 5FU and folinic acid had less survival rate than those who took 5FU alone [20]. However, this result was opposed in 2015 by Mayer, Benjamin et al [21] study, which showed for the first time, that the addition of folinic acid to adjuvant chemotherapy regiments had given a better outcome among colon cancer (CC) patients, especially among the elderly.

3.3. Folate & CRC/A recurrence

Several studies also discussed the relationship between folate supplementation and CRC recurrence, yielding different results as many of them found no protective role against colorectal adenoma (CRA) and

Table 2
Folate & CRC/A recurrence.

Study	Sample size (N)	Dose (MG/DAY)	Duration	Effect on CRA recurrence
Greece (1994) (26)	60	1	2 years (YR)	No effect
AFPPS (2007) (12)	1021	1	6 YR	67% increased risk
Detroit VA (2008) (28)	94	5	3 YR	46% decreased risk
(UKCAP) (2008) (27)	853	0.5	3 YR	No effect
(NHS-HPFS) (2009) (22)	672	1	3 YR	No effect
Ibrahim, Ezzeldin M, and Jamal M Zekri Meta-analysis (2010) (25)	1580	1	1-3 YR	No effect
Combined Analysis of AFPPS, NHS-HPFS, & UKCAP (2011) (30)	2632	0.5–1	6–42 months	No effect
Meta-Analysis of AFPPS, NHS-HPFS, & UKCAP (2013) (31)	2632	0.5–1	3-6 YR	Increased risk
Focus CONSORTIUM (2020) (19)	2024	–	[a]	No effect

[a] The **FOCUS consortium** includes 6 cohorts.
- The COLON [34](n = 1094) and EnCoRe [35](n = 297) studies are ongoing prospective cohort studies that recruit newly diagnosed colorectal cancer patients since 2010 and 2012, respectively. (from eleven hospitals in the Netherlands for the COLON study and from three hospitals in the Netherlands for the EnCoRe study).
- CORSA [36](n = 209) is an ongoing study since 2003, recruiting colorectal cancer patients in cooperation with the province-wide screening project "Burgenland Prevention Trial of Colorectal Disease with Immunological Testing" (B-PREDICT) using fecal occult blood testing (FOBT).
- ColoCare [36] is an ongoing, international, prospective cohort study. Patients were recruited since 2010 at the University Hospital of Heidelberg and the National Center for Tumor Diseases in Heidelberg, Germany(n = 260) (ColoCare HD). ColoCare patients were also recruited since 2015 at Huntsman Cancer Institute(n = 46) (Salt Lake City, U.S.) (ColoCare HCI) and since 2007 at Fred Hutchinson Cancer Research Center(n = 118) (Seattle, U.S.) (ColoCare FHCRC).

carcinoma (CRC) [22–25]. The ukCAP [26] & Greece [27] trials found that folate supplementation with 0.5–1 mg/day had no effect on CRA recurrence. However, the Detroit VA trial [28]; in which individuals with resected adenoma were supplied with 5 mg/day of vit-B9 for 3 years, reported a significant decrease in CRA recurrence. In Nurses' Health Study/Health Professionals Follow-Up Study (NHS-HPFS) [22], although 1 mg/day supplementation of vit-B9 within 3 years was fond to decrease the CRA risk in those with low baseline plasma folate concentration(≤7.5 ng/ml), the overall effect didn't affect CRA recurrence. Moreover, the Aspirin/Folate Polyp Prevention study (AFPPS) [12] stated that 1 mg/day supplementation of folate for 6years was associated with 67% increased risk of CRA recurrence. In Ding, Hui et al. study, higher plasma folate concentrations were associated with decreased CRA occurrence and recurrence [29].In 2011, a combined analysis of the AFPPS, NHS-HPFS, & ukCAP studies was performed and determined no effect of folate supplementation on CRA recurrence [30]. In 2013, a meta-analysis of the mentioned studies found a borderline increased risk of CRA recurrence [31].This can be explained by the presence of pre-existing undiagnosed neoplastic foci [32] or can be attributed to genotype variations of folate metabolism as a significant decrease in CRC recurrence was found among patients heterozygous for MTRR A66G and MTHFR A1298C polymorphisms. Moreover, a significant reduction in recurrence was also seen in MTRR A66G heterozygotes who received folate supplementation but not in those who didn't receive it. However, MTHFR C677T and MTR A2756G polymorphism had no significant reduction, in addition to the TSER, TSER 3R G > C and TS14de16 variants that had no effect on recurrence at all [33]. These findings suggest that genotype variations of folate metabolism may affect the development of CRA [33] (Table 2).

4. Conclusion

Our article supports the protective role of folic acid in the absence of tumor foci and its cancerous effect in the presence of such foci; which may explain the different results of folate effect on CRC risk and support the role of *anti*-folate agents as chemotherapy drugs. However, the role of folate in preventing recurrence and improving survival rates remains unresolved and requires further evidence from clinical trials, with a possible potential role of folate metabolism genotype variations.

Ethical approval

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Author contributions

HK: is the mentor, drafted the manuscript.
RD, TS, YS, ZA & JE: collected the data and participated in revising the article.
ZA: is the guarantor and supervisor & critically revised the article.
MG: is the oncologist & participated in revising the article.

Registration of research studies

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Guarantor

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Consent

NA.

Declaration of competing interest

No conflict of interest.

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Abbreviations

CRC	Colorectal cancer
CRA	Colorectal adenoma
FA	Folic acid
RCT	Randomized control trial
5FU	5-Fluorouracil

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