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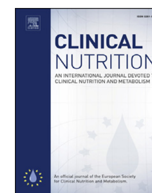

Original article

High serum folate might have a potential dual effect on risk of colorectal cancer

Feng-Fan Chiang [a], Shih-Chien Huang [b, c], Hwei-Ming Wang [d], Fang-Pei Chen [b], Yi-Chia Huang [b, c, *]

[a] Division of Colorectal Surgery, Department of Surgery, Taichung Veterans General Hospital, Taichung, Taiwan
[b] School of Nutrition, Chung Shan Medical University, Taichung, Taiwan
[c] Department of Nutrition, Chung Shan Medical University Hospital, Taichung, Taiwan
[d] Department of Colorectal Surgery, China Medical University Hospital, Taichung, Taiwan

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SUMMARY

Background & aims: The possible dual role of serum folate in the development and progression of colorectal cancer (CRC) has not been well established in human studies. This study investigated the association between serum folate and the risk of CRC in subjects with CRC or colorectal adenomatous polyps (AP, a precursor of CRC), and healthy subjects.
Methods: This study has a case–control design. Two hundred and thirty-seven men and 171 women were recruited with 156 subjects in the CRC group, 70 subjects in the AP group and 182 healthy subjects in the control group.
Results: The risk of CRC was significantly increased in the third (OR, 3.46; 95% CI, 1.16–10.34) and fourth (OR, 4.86; 95% CI, 1.42–16.58) quartiles of serum folate concentration after adjusting for potential confounders among subjects with AP or CRC. Furthermore, serum folate concentration had no significant effect on the risk of CRC among subjects in the control and CRC groups.
Conclusions: Higher serum folate concentration was significantly correlated with increased CRC risk in subjects with AP, while serum folate had no effect on CRC risk in healthy controls. Serum folate might possess potential dual modulatory effects on the risk of CRC.
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1. Introduction

Colorectal cancer (CRC) is the 3rd and 2nd most commonly diagnosed cancer worldwide in men and women, respectively [1]. Colorectal polyps are classified as hyperplastic or adenomatous based on the histologic type, and adenomatous polyps (AP) are considered precursors of most colorectal cancers [2,3]. Among the various nutritional factors which are related to the CRC risk, the feature of folate in the development and progression of CRC warrants attention. To investigate the association between folate status and the risk of CRC, dietary folate intake rather than serum folate concentration has been extensively studied [4]. However, there are few data on the effects of serum folate levels on the risk of CRC. Low serum folate level has been shown to be a significant risk factor for the risk of CRC [5,6], while other studies indicated that low serum folate level had a protective effect [7,8] or no effect on the risk of CRC [9,10]. Further studies are therefore warranted to verify the relationship between serum folate concentration and CRC risk.

Folate is an essential cofactor for the de novo biosynthesis of purines and thymidylate; therefore, folate deficiency may cause a defect in DNA synthesis in tissue with rapidly replicating cells. This may explain why low serum folate concentration increased the risk of CRC [6,8]. However, folate might possess dual modulatory effects on CRC development and progression; folate deficiency may inhibit while folate supplementation may promote the progression of established colorectal neoplasms [11–15]. Studies indicated that tumor growth might be inhibited by ineffective DNA synthesis resulting from folate deficiency [13,16,17]. Although the dual modulatory effect of folate on colorectal carcinogenesis has been established in animal studies [18–20], the possible dual feature of serum folate in CRC development and progression has not been well described in human studies. Thus, the study presented here

* Corresponding author. No. 110, Sec 1, Jianguo N. Rd., School of Nutrition, Chung Shan Medical University, Taichung 402, Taiwan.
E-mail address: ych@csmu.edu.tw (Y.-C. Huang).

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investigated the association of serum folate with the risk of CRC in subjects with CRC or AP (a precursor of CRC), and healthy subjects.

2. Subjects and methods

2.1. Subjects

Consecutive patients were recruited from the division of colorectal surgery of Taichung Veterans General Hospital, Taiwan if they were confirmed to have either colon or rectal cancer (International Classification of Diseases 9, codes 153 and 154, respectively) (CRC group). Patients were excluded if they were pregnant, lactating, received chemotherapy, had history of cardiovascular disease, liver or renal diseases, diabetes, alcoholism, attenuated adenomatous polyposis coli or inflammatory bowel disease, or were taking any medication which could influence homocysteine and folate status. Two study oncologists reviewed patients' medical records for diagnostic confirmation and staging. Healthy subjects were recruited from the health management center of Taichung Veterans General Hospital, Taiwan. Each subject was referred for colonoscopy. If subjects were identified by colonoscopy as having at least one or more histologically confirmed colorectal AP, they were assigned to the AP group; otherwise, they were allocated to the control group. Subjects in the AP and control groups were excluded when they had history of gastrointestinal disorder, cardiovascular diseases, liver or renal diseases, diabetes, cancer, alcoholism, or other metabolic diseases. Each subject signed the informed consent. The Institutional Review Board of Taichung Veterans General Hospital approved this study.

2.2. Data collection and biochemical measurements

All subjects' age, gender, height, weight, smoking and drinking habits and use of medications were recorded. Subjects' height and weight were used to calculate their body mass index (BMI, kg/m^2). Systolic and diastolic blood pressure (SBP and DBP) was measured after a resting period of at least 5 min.

Each subject's fasting venous blood samples were drawn in vacutainer tubes containing an appropriate anticoagulant or no anticoagulant. Serum or plasma was separated within 30 min after blood was collected and then frozen (−80 °C) until analysis. Serum creatinine was assessed using an automated biochemical analyzer. Samples of plasma homocysteine and PLP were prepared under yellow light to avoid photodestruction and measured by high performance liquid chromatography as previously described [21,22]. Serum folate was analyzed using standard competitive immunochemiluminometric methods on a Chiron Diagnostics ACS:180 Automated Chemiluminescence System (Chiron Diagnostics Corporation, USA).

The genomic DNA purification kit (Blood total DNA auto kit, TANBead, Taiwan) was used to extract DNA from frozen peripheral blood lymphocytes. The 5, 10-methylenetetrahydrofolate reductase (MTHFR) 677C→T gene polymorphism was amplified by polymerase chain reaction. The amplified DNA fragment (198 bp) was then digested by the H*inf*I restriction enzyme (New England BioLabs, Ipswich, MA) and subsequent electrophoresis in a 3% agarose gel [23].

2.3. Statistical analyses

The SAS statistical software package (version 9.3; Statistical Analysis System Institute Inc., Cary, NC, USA) was used for all data analyses. Demographic characteristics and biochemical data were compared for significance using one-way analysis of variance or Kruskal–Wallis test. Chi-square or Fisher's exact tests were used for the analysis of categorical variables. Adjusted odds ratios (OR) with 95% confidence intervals (CI) for CRC risk were calculated from unconditional logistic regression models using serum folate and the quartiles of serum folate concentration, based on the distribution of the AP and CRC subjects or the control and CRC subjects. Statistical significance was defined as a two-sided $p < 0.05$.

3. Results

Table 1 shows subjects' demographic and health characteristics. Two hundred and thirty-seven men and 171 women were in this study with 156 subjects in the CRC group, 70 subjects in the AP group and 182 subjects in the control group. Subjects' ages ranged from 30 to 79 years with a mean age of 53.4 ± 11.0 y. No significant differences were observed in gender, BMI, plasma PLP concentrations, and distribution of the three variants of the MTHFR 677C→T genotypes among the 3 groups. Subjects in the CRC group had significantly older age, higher SBP and plasma homocysteine levels compared with subjects in the other two groups. A significantly higher serum folate level was observed in CRC subjects when compared to AP and control subjects. The distribution of genotypes among the 3 groups of subjects was conformed with the Hardy–Weinberg equilibrium.

We calculated the risks of CRC according to the distribution of subjects in the AP and CRC groups (Table 2) and subjects in the control and CRC groups (Table 3). Increased plasma homocysteine and serum folate had significant positive effects on the risk of CRC among subjects in the AP and CRC groups with or without adjusting for confounders (Table 2). We then further calculated the OR using the quartiles of serum folate based on the distribution of AP and CRC subjects. The CRC risk was significantly increased in the third (serum folate concentration, 13.55–23.61 ng/mL; OR, 3.46; 95% CI, 1.16–10.34) and fourth (serum folate concentration > 23.61 ng/mL; OR, 4.86; 95% CI, 1.42–16.58) quartiles of serum folate concentration following adjustment for age, gender, BMI, SBP, serum creatinine concentration, smoking and drinking habits, MTHFR 677C→T mutation, and plasma homocysteine and PLP concentrations (Table 2). Interestingly, serum folate concentration had no effect on the risk of CRC among subjects in the control and CRC groups (Table 3). However, plasma homocysteine was still a significant risk factor for CRC after adjusting for potential confounders among subjects in the control and CRC groups (Table 3).

Table 1
Demographic and health characteristics of subjects.[a]

Parameters	CRC (n = 156)	AP (n = 70)	Control (n = 182)
Age (y)	59.12 ± 10.92a	52.73 ± 9.51c	48.75 ± 9.24b
Male/Female	94/62	52/18	91/91
BMI (kg/m^2)	24.13 ± 3.25	25.07 ± 3.23	24.09 ± 3.74
Blood pressure			
SBP (mmHg)	140.37 ± 17.62a	135.25 ± 24.46b	118.12 ± 16.98c
DBP (mmHg)	82.71 ± 11.29a	85.54 ± 15.69a	75.78 ± 12.18b
Serum creatinine (mg/dL)	0.84 ± 0.31b	0.92 ± 0.22a	0.81 ± 0.20b
Plasma homocysteine (μmol/L)	15.27 ± 5.61a	13.28 ± 4.94b	11.63 ± 4.97c
Serum folate (ng/mL)	19.78 ± 12.72a	13.29 ± 9.14b	15.27 ± 8.31b
Plasma PLP (nmol/L)	91.51 ± 85.93	103.43 ± 95.98	84.47 ± 77.39
MTHFR 677C→T (n) CC/CT/TT	84/64/8	44/26/0	91/73/18
Smoking habit (n, %)	25, 16.03%	24, 34.29%	34, 18.68%
Drinking habit (n, %)	13, 8.33%	23, 32.86%	48, 26.37%

CRC, colorectal cancer; AP, adenomatous polyps. *MTHFR*, methylenetetrahydrofolate reductase; BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.
Values in a row with different superscript letters are significantly different, $p < 0.05$.
[a] Values are means ± standard deviation.

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