Short Communication

Blood Folate Levels and Risk of Liver Damage and Hepatocellular Carcinoma in a Prospective High-Risk Cohort

Tania M. Welzel,[1] Hormuzd A. Katki,[1] Lori C. Sakoda,[1] Alison A. Evans,[2] W. Thomas London,[3] Gang Chen,[2] Sean O'Broin,[4] Fu-Min Shen,[5] Wen-Yao Lin,[6] and Katherine A. McGlynn[1]

[1]Division of Cancer Epidemiology and Genetics, Department of Health and Human Services, National Cancer Institute, NIH, Bethesda, Maryland; [2]Drexel School of Public Health; [3]Fox Chase Cancer Center, Philadelphia, Pennsylvania; [4]St. James Hospital, Dublin, Ireland; [5]Fudan Medical University, Shanghai, China; and [6]Haimen City Center for Disease Control, Haimen City, China

Abstract

Background: **Studies in experimental animals suggest that low folate levels may play a role in liver damage and hepatocarcinogenesis. To examine this association in humans, folate levels in blood and risk for subsequent liver damage and hepatocellular carcinoma (HCC) were assessed in a population at high risk of liver cancer in China.**
Methods: **Four hundred fifteen hepatitis B surface antigen–positive participants of the Haimen City Cohort were prospectively followed between 1998 and 2002. Serum and RBC folate levels were determined at baseline. Alanine aminotransferase (ALT) and hepatitis B virus DNA levels were measured semiannually. Logistic regression modeling was used to examine the presence of hepatitis B virus DNA and HCC, whereas linear regression with a log-link function was used to examine ALT levels.**
Results: **There was a statistically significant inverse association between serum folate level and ALT level. ALT levels decreased with each quartile increase in serum folate (adjusted odds ratio, 0.86; 95% confidence interval, 0.76-0.97 for the highest compared with the lowest quartile; P_{trend} = 0.002). After exclusion of three persons with prevalent HCC, 20 (4.9%) of the 412 study participants developed HCC during follow-up, with a median time between enrollment and HCC diagnosis of 2.66 years (interquartile range, 1.8-4.1). When comparing persons in the lowest quartile RBC folate to persons in all other quartiles, the analysis found that higher RBC folate levels were associated with reduced risk of hepatocarcinogenesis (odds ratio, 0.33, 95% confidence interval, 0.13-0.86; P_{trend} = 0.02).**
Conclusions: **This study suggests that increased folate levels in humans may be inversely associated with the development of liver damage and HCC.** (Cancer Epidemiol Biomarkers Prev 2007;16(6):1279–82)

Introduction

Hepatitis B virus (HBV)–related liver disease and hepatocellular carcinoma (HCC) are major public health problems in China (1). In addition to chronic HBV infection (2), several other environmental and nutritional cofactors may modify or contribute to risk of liver disease and hepatocarcinogenesis (3, 4). One such factor may be folate, a water-soluble B vitamin naturally occurring in several foods. Folate represents an important factor for DNA methylation and replication during cell regeneration, a role that has received increasing attention in human carcinogenesis (5-8). In particular, in several animal studies, low folate levels have been linked to oxidative stress, liver damage, and hepatocarcinogenesis; however, no studies have yet investigated this association in humans (9-11). As recent studies indicate that large proportions of the Chinese population may have low folate levels (12), we examined the relationships among serum and red blood cells (RBC) folate levels, a measure of HBV replication (HBV DNA), an indicator of liver damage [alanine aminotransferase (ALT) levels], and HCC in a high-risk population in Haimen City, China.

Materials and Methods

Study Population. Details of the Haimen City Cohort study of HCC have been published previously (13, 14). Briefly, between February 1992 and December 1993, 90,836 persons were enrolled in the study to examine the relationships between HBV infection, environmental factors, genetic events, and gene-environment interactions in the etiology of HCC. Study participants donated a blood sample and responded to a risk factor questionnaire. In 1998, a representative sample of 415 persons with chronic HBV infection (i.e., seropositive for hepatitis B surface antigen positive) was randomly selected and followed to investigate the association of folate status, HBV replication, and risks of liver damage and HCC. Serum and RBC folate levels were determined at baseline, whereas ALT, a marker of liver damage, and HBV DNA, an indicator of HBV replication, were measured semiannually over the 4-year study period. HCC diagnoses were ascertained by α-fetoprotein elevation (>400 ng/mL), and/or liver imaging, clinical criteria, histologic exam, or by death certificate with postmortem interviews of family members. Study participants diagnosed with HCC less than 1 year after study enrollment were excluded to avoid misclassification of prevalent tumors. Study protocols and materials were approved by the Institutional

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Requests for reprints: Tania M. Welzel, Division of Cancer Epidemiology and Genetics, Department of Health and Human Services, National Cancer Institute, NIH, EPS, Suite 550, 6120 Executive Boulevard, Bethesda, MD 20892-7234. Phone: 301-451-5033. E-mail: tmwelzel@web.de or welzelt@mail.nih.gov

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Review Boards of Fox Chase Cancer Center, the Haimen City Antiepidemic Station (which subsequently became the Haimen Center for Disease Control), and Shanghai Medical University.

Laboratory Methods. Within 24 h of blood collection, serum was separated from whole blood. Hepatitis B surface antigen was tested by RIA at the Haimen City Center for Disease Control at the time of collection. Serum aliquots were stored at −20°C in Philadelphia and retrieved in 2003 for viral load testing by real-time PCR. The method for quantifying HBV DNA has been described previously (15). Briefly, HBV DNA was extracted from human serum using the QIAamp DNA Blood Mini kit (Qiagen) following the manufacturer's protocol. The prepared DNA samples were stored at −20°C until use. The Taqman PCR assay was based on that published by Loeb et al. (16) that used PCR primers amplifying a conserved region of the HBV X gene. The ABI Prism 7900HT Sequence Detection System (Applied Biosystems) was used for detection and quantification of HBV DNA. The limit of detection for the assay was 20 copies per reaction or 1.6×10^3 copies/mL. Samples were tested in duplicate and repeated if there was a difference of >0.5 cycles between the replicates. Each PCR run contained negative controls and a standard curve of serially diluted HBV plasmids in duplicate.

Serum and RBC folate were determined at the St. James Hospital (Dublin, Ireland) using the *Lactobacillus casei* assay as described previously (17, 18). Serum folate and red cell folate concentrations assayed by the *L. casei* microbiological assay have compared well with concentrations obtained with a new-order reference method employing Stable-Isotope-Dilution Tandem Mass Spectrometry (19, 20). To ensure the stability of blood folate concentrations, serum was separated from whole blood and hemolysates were prepared from EDTA-anticoagulated whole blood within 24 h of collection. Hemolysates for determination of RBC folate were prepared by 10-fold dilution of whole blood in 10 g/L ascorbic acid followed by incubation at room temperature for 60 min. All specimens collected in the study were stored at −80°C, transported to the laboratory on dry ice, and again stored at −80°C until analysis. Each specimen was tested in duplicate, using two different dilutions. Folate assay performance was monitored using controls that were constituted using both serum and ethylenediamine tetraacetic acid (K_2 EDTA) anticoagulated whole blood from both normal donor volunteers and from patients under investigation with anemia. Control specimens were stored in aliquots at −80°C. The assay displayed excellent intra-assay/interassay reproducibility based on the duplicate testing of patient samples and monthly means for both serum (%CV, <4%) and whole blood folate (%CV, <5%) controls, resulting in an overall assay repeat rate of 0%. Serum ALT was tested using the standard kinetic method.

Statistical Analyses. Baseline characteristics were compared between men and women using *t* tests. Logistic regression was used to examine the presence of HCC and HBV DNA and linear regression with a log-link function to examine ALT levels in relation to folate levels. Analyses were adjusted for sex, smoking, age, alcohol consumption, and presence of HBV DNA in analyses of all participants, and analyses were stratified by gender. Serum and RBC folate levels (in quartiles) were rounded to the next 0.5 or 10, respectively. To account for within-person correlation of outcomes, the regressions used generalized estimating equations (21) with working independence correlations and empirical robust SEs. Wald χ^2 tests were used to calculate two-sided *P* values and 95% confidence intervals (95% CI). Intraclass correlations were calculated to estimate the within-subject variability of HBV DNA and ALT measures overtime. Statistical analyses were done using SAS version 9.1 (SAS Institute) and MATLAB R2006a (The Mathworks, Inc.).

Results

The baseline characteristics of the study population are summarized in Table 1. Three participants with prevalent HCC were excluded from the analysis, leaving 412 hepatitis B surface antigen–positive persons, of whom 229 (55.6%) were male and 183 (44.4%) were female. The mean age of the male and female participants did not differ (49.9 and 49.9 years; $P = 0.98$). Men were significantly more likely than women to consume alcohol (51% versus 11%; $P < 0.0001$) and to smoke cigarettes (45% versus 2%; $P < 0.0001$). Men were also significantly more likely than women to be HBV DNA positive (29% versus 16%; $P < 0.0001$), but mean HBV DNA titer did not differ by gender (2.2 and 2.3 $\log_{10}$ copies/mL; $P = 0.24$, respectively). Compared with women, men had significantly higher ALT levels (41 versus 25 IU/L; $P < 0.0001$) but lower serum folate levels (9.1 versus 11.9 μg/L; $P = 0.0001$) and lower RBC folate levels (366 versus 436 μg/L; $P < 0.0001$).

Table 1. Characteristics of 412 hepatitis B surface antigen–positive study participants

Variable	Males (*n* = 229)	Females (*n* = 183)	*P*
	n (%)	*n* (%)	
Age, mean ± SD (y)	49.9 (9.0)	49.9 (7.8)	0.98
Alcohol consumption			
Current drinker	116 (51)	21 (11)	<0.0001
Nondrinker	113 (49)	162 (89)	
Cigarette smoking			
Current smoker	104 (45)	4 (2)	<0.0001
Nonsmoker	125 (56)	179 (98)	
HBV DNA			
Positive	67 (29)	30 (16)	<0.0001
Negative	162 (71)	153 (84)	
HBV DNA			
Mean titre ± SD (copies/mL)	595 ± 917	585 ± 800	0.24
Mean titre ± SD ($\log_{10}$ copies/mL)	2.2 ± 0.8	2.3 ± 0.7	0.24
Mean ALT ± SD (IU/L)	41 ± 39	25 ± 23	<0.0001
Folate (μg/L)			
Mean serum folate ± SD	9.1 ± 1.6	11.9 ± 1.5	<0.0001
Mean RBC folate ± SD	366 ± 1.34	436 ± 1.34	<0.0001
HCC developed during study			
Yes	12 (5.2)	8 (4.4)	0.68
No	217 (94.8)	175 (95.6)	

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Table 2. Relationship of HBV DNA and ALT to serum and RBC folate levels

	n	HBV DNA* (copies/mL)		ALT† (IU/L)	
		OR (95% CI)	P_{trend}	OR (95% CI)	P_{trend}
Serum folate-all (μg/L)					
Q1: <7.5	526	Referent	0.12	Referent	0.002
Q2: 7.5-10.4	556	1.33 (0.73-2.42)		1.02 (0.91-1.15)	
Q3: 10.5-14.4	561	1.39 (0.72-2.67)		0.89 (0.79-1.00)	
Q4: ≥14.5	514	1.70 (0.87-3.33)		0.86 (0.76-0.97)	
Serum folate-women (μg/L)					
Q1: <7.5	273	Referent	0.22	Referent	0.004
Q2: 7.5-10.4	322	1.43 (0.39-2.57)		1.03 (0.86-1.24)	
Q3: 10.5-14.4	307	1.55 (0.28-2.91)		0.85 (0.73-0.99)	
Q4: ≥14.5	284	1.61 (0.17-3.16)		0.85 (0.72-1.01)	
Serum folate-men (μg/L)					
Q1: <7.5	240	Referent	0.85	Referent	0.04
Q2: 7.5-10.4	217	0.81 (0.38-1.73)		0.99 (0.85-1.16)	
Q3: 10.5-14.4	281	0.86 (0.39-1.89)		0.91 (0.77-1.08)	
Q4: ≥14.5	233	0.90 (0.41-2.00)		0.83 (0.70-1.00)	
RBC folate-all (μg/L)					
Q1: <320	578	Referent	0.68	Referent	0.92
Q2: 320-399	492	0.55 (0.28-1.07)		1.02 (0.87-1.20)	
Q3: 400-499	612	0.92 (0.49-1.75)		1.02 (0.88-1.19)	
Q4: ≥500	475	0.73 (0.35-1.54)		0.97 (0.79-1.20)	
RBC folate-women (μg/L)					
Q1: <320	327	Referent	0.91	Referent	0.65
Q2: 320-399	286	0.84 (0.26-2.69)		1.06 (0.88-1.29)	
Q3: 400-499	296	0.95 (0.28-3.18)		0.94 (0.79-1.12)	
Q4: ≥500	277	0.90 (0.27-2.96)		1.01 (0.85-1.20)	
RBC folate-men (μg/L)					
Q1: <320	248	Referent	0.82	Referent	0.92
Q2: 320-399	246	0.66 (0.30-1.45)		1.02 (0.87-1.20)	
Q3: 400-499	241	0.51 (0.21-1.23)		1.02 (0.88-1.19)	
Q4: ≥500	236	1.01 (0.46-2.21)		0.97 (0.79-1.20)	

Abbreviations: Q, quartile; OR, odds ratio.
*Adjusted for year, age, sex, smoking and drinking status, and ALT.
† Adjusted for sex, age, smoking, alcohol consumption, and presence of HBV DNA.

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Overall median RBC and serum folate levels were 400 μg/L (interquartile range, 320-500 μg/L) and 10.5 μg/L (interquartile range, 7.5-14.5 μg/L), respectively. Intraclass correlation coefficients indicated a good within-subject consistency of ALT and HBV DNA measurements over time (r = 0.65 and 0.83, respectively). During study follow-up, 20 (4.9%) of the 412 participants developed HCC, with a median time between enrollment and HCC diagnosis of 2.66 years (interquartile range, 1.8-4.1). HCC incidence did not differ significantly between the men and women (5.2% versus 4.4%; P = 0.68).

The relationships of folate to HBV DNA, ALT, and HCC risk, adjusted for age, gender, HBV DNA level, and alcohol consumption, are presented in Table 2. No significant association was found between serum or RBC folate level and HBV DNA titer in either the overall or the stratified analyses. Although women had higher serum and RBC folate levels and lower HBV DNA levels, the associations between folate and HBV DNA were not statistically significant in any gender-specific analysis.

There was a statistically significant inverse association between serum folate level and ALT level, as ALT levels decreased with each quartile increase in serum folate (odds ratio, 0.86; 95% CI, 0.76-0.97 for the highest compared with the lowest quartile; P_{trend} = 0.002). This inverse trend between serum folate and ALT remained significant in the analyses stratified by gender (P_{trend} = 0.004 for women and P_{trend} = 0.04 for men, respectively). No significant association was found between serum ALT and RBC folate, either in the overall or in the stratified analyses.

Compared with participants in the lowest quartile of serum folate, the odds of developing HCC decreased as folate level increased. The association, however, did not attain statistical significance (P_{trend} = 0.36 and 0.13 for serum and RBC folate, respectively). When comparing persons in the lowest quartile RBC folate with persons in all other quartiles, however, the results were consistent with a role of RBC folate levels in hepatocarcinogenesis (odds ratio, 0.33; 95% CI, 0.13-0.86; P_{trend} = 0.02; Table 3).

Discussion

This is the first study to report on the role of folate in liver damage and hepatocarcinogenesis in humans in a population at high risk of developing HCC. The results of this study suggest an inverse association between serum folate levels and liver damage as assessed by serum ALT levels. Furthermore, the results suggest that high RBC folate levels may be associated with decreased risk for HCC as shown in an analysis that compared subjects in the lowest quartile with all other study subjects.

As anticipated, the female study participants were more likely than the males to be HBV DNA(−) and to have lower ALT levels. It has been reported previously that HBV-infected women remain chronically infected for shorter periods and

Table 3. Relationship of serum and RBC folate in quartiles to development of HCC

	n	RR (95% CI)	P
Serum folate			
Quartile 1	526	Referent	
Quartiles 2-4	1,631	0.56 (0.21-1.50)	0.25
RBC folate			
Quartile 1	578	Referent	
Quartiles 2-4	1,579	0.33 (0.13-0.86)	0.02

are more likely to control viral replication, although reasons for this gender difference are not well understood (22, 23). A positive association between HBV viral load and HCC risk has been shown previously for this study population (2); however, in the current analysis, there was no association between folate levels and HBV replication, eliminating the possibility of reverse causality (i.e. higher folate levels in patients with high viral levels and more severe liver injury that could increase folate levels).

The female participants also had significantly higher baseline folate levels than did the males, similar to what has been described in other Asian populations (24). Whether the discrepancy in levels reflects dietary differences or other influences is not certain. It is possible, though, that the difference in folate levels is related to the significantly (~4.5-fold) higher percentage of alcohol consumption among the male participants. Alcohol is known to adversely affect the bioavailability and metabolism of folate (25, 26) and may, as a result, contribute to increased homocysteine levels (25) that favor liver damage through oxidative stress and profibrogenic effects (25-27).

Regardless of whether alcohol affected the folate levels in males, in the adjusted analysis, the significant association of folate status and liver damage was independent of other known or potential risk factors, including age, gender, alcohol consumption, smoking, and HBV replication. Liver damage itself could lead to slightly increased serum folate levels, which however, would only serve to make the observed association stronger. These findings are supported by prior studies in experimental animals that reported an increased risk of liver damage, impaired liver regeneration, and hepatocarcinogenesis in folate-deficient mice (9-11). As very few subjects in this population were frankly folate deficient, the results suggest that lower folate levels, even if they are not in the deficient range, may confer an increased risk for liver damage in humans. In parallel to these results, several studies have described an association of folate intake or blood folate levels with several human cancers (6-8), further supporting the importance of folate in DNA synthesis and replication, cell division, and to prevent changes to DNA that may lead to cancer.

The current study had several advantages, including a prospective design, a high-risk population, direct measurement of folate status, and a high completeness of follow-up visits, missing <15% of the study populations' 2,157 person-visits during the study period. Possible limitations include a single assessment of folate status at baseline and a follow-up that may have been of insufficient length to assess fully a relationship between folate status and development of HCC as the number of cancer cases during the 4 year study period was not large.

In summary, this is the first study to show an association in humans of serum folate levels and liver damage and possibly HCC. In regard to the global HCC burden and the possible chemopreventive role of folate, further studies on the role of folate in liver cancer in humans should certainly be encouraged. These studies might consider determining folate levels throughout the study and including a larger population to examine liver cancer as an outcome.

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