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Choline and betaine intake and the risk of colorectal cancer in men

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Abstract

Dietary choline and betaine have been hypothesized to decrease the risk of cancer because of their role as methyl donors in the one-carbon metabolism. However, it remains unknown whether dietary intake of choline and betaine is associated with colorectal cancer risk. We prospectively examined the associations between dietary choline and betaine intake and risk of colorectal cancer in men in the Health Professionals Follow-up Study. We followed 47,302 men and identified a total of 987 incident colorectal cancer cases from 1986 to 2004. We assessed dietary and supplemental choline and betaine intake every four years using a validated semi-quantitative food frequency questionnaire. The Cox proportional hazards model was used to estimate multivariate relative risks (RRs) and 95% confidence intervals (95% CIs). All statistical tests were two-sided. We did not find any statistically significant associations between choline intake or betaine intake and risk of colorectal cancer. Comparing the top quintile with bottom quintile, multivariate RRs (95% CI) were 0.97 (0.79-1.20; P*trend* = 0.87) for choline intake and 0.94 (0.77-1.16; P*trend* = 0.79) for betaine intake. Similarly, we observed no associations between colorectal cancer risk and choline from free choline, glycerophosphocholine, phosphocholine, phosphatidylcholine, or sphingomyelin. Our data do not support that choline and betaine intake is inversely associated with colorectal cancer risk.

Keywords

Choline; Betaine; Colorectal Cancer

Introduction

Choline is important for the structural integrity of cell membranes, methyl metabolism, cholinergic neurotransmission, transmembrane signaling, and lipid and cholesterol transport and metabolism, because it is a precursor for acetylcholine, phospholipids, and the methyl donor betaine (1). Like folate, once choline is oxidized to betaine, it can provide one-carbon units in the conversion of homocysteine to methionine, generating S-adenosylmethionine (SAM), the universal methyl donor (1).

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Despite the role of choline and betaine as methyl donors in the one-carbon metabolism, few studies have examined the associations between choline or betaine intake and cancer risk (2-4), partly due to lack of choline and betaine food composition tables until recently (5). We previously found increased risk of colorectal adenoma with increasing intake of choline, but not of betaine (6). Here we examine the association between choline and betaine intake and colorectal cancer risk.

Materials and Methods

The Health Professionals Follow-up Study (HPFS) was initiated in 1986 when 51,529 male health professionals aged 40 to 75 years returned a mailed questionnaire. We excluded participants who had cancer, left extensive food items blank, or had implausible energy intake at baseline in 1986. As a result, 47,302 men were included. This study was approved by the Institutional Review Boards of the Harvard School of Public Health (Boston, MA).

Dietary information was collected from participants using validated semi-quantitative food frequency questionnaires in 1986 and every four years thereafter. Responses on frequencies of a specified serving size for each food item were converted to average serving per day. The quantities of choline and betaine from foods were calculated by multiplying average serving per day by the nutrient content of one serving of that food (5,7). Because supplements contributed little to total intake, we presented dietary choline and betaine intake (from foods only) as main results. For total intake (from foods and supplements), we took into account current use of supplements and brand and type of multivitamins (asked every 2 years).

Information on weight, physical activity, aspirin use, current multivitamin use, family history of colorectal cancer in parents and siblings, and endoscopy history were updated every two to four years. Duration of multivitamin use, average number of cigarettes smoked per day in the age ranges of <15, 15-19, and 20-29 years, and height were assessed at baseline.

We obtained self-reported information on the occurrence of colorectal cancer on each follow-up questionnaire and asked participants (or next-of-kin for those who had died) for permission to access medical records to confirm the cancer diagnosis. In addition, the National Death Index (8) was used to identify fatalities.

Participants were categorized using quintiles on the basis of the distribution of intakes. Intakes of choline, betaine, and other nutrients were energy-adjusted using the residuals from the regression of nutrient intake on total energy intake (9). Relative risk (RR) and 95% confidence interval (95% CI) were calculated using the Cox proportional hazards model (10), stratified by age and calendar year, using SAS 9.1 (SAS institute, Cary, NC). Person-years of follow-up were estimated from the date that the baseline questionnaire was returned to the date of colorectal cancer diagnosis, date of death, or end of follow-up (January 31, 2004), whichever came first. In the multivariate models, we adjusted for possible risk factors listed in the footnote to Table 1. As the main analytic strategy, the cumulative average choline and betaine intakes were calculated from all available dietary questionnaires (11). We also examined baseline intake and latency between intake and colorectal cancer diagnosis, methods of which are described in footnotes to Table 1.

For the test for trend, participants were assigned the median value of their intake category, and this variable was tested with the Wald test. A test for interaction was conducted using the likelihood ratio test by comparing the model fit including the cross-product term of a continuous exposure variable with a modifier variable with the model fit excluding the cross-protect term.

Results

During 18 years of follow-up, a total of 987 colorectal cancer cases were documented. We found no association between colorectal cancer risk and intake of choline or betaine from either food (>97% of choline or betaine intake)(Table 1) or supplements (data not shown). Choline from each individual food source was not associated with risk of colorectal cancer (Table 1). When we examined choline intake 12-16 years prior to diagnosis, there was no significant trend in the association (P*trend* = 0.76), although the wide confidence interval indicated that some benefit cannot be excluded. We found no associations between choline or betaine intake and risk of distal (n=303 cases), proximal (n=321 cases), or rectal cancers (n=210 cases) (P*trend* ≥ 0.41).

We also did not find that any associations varied by folic acid fortification period (pre-fortification period: n = 636 cases; and post-fortification period: n=296 cases) (data not shown).

When we stratified by cumulative average alcohol intake, baseline folate intake, family history of colorectal cancer, body mass index, and smoking habits, we found no association between either choline or betaine intake and colorectal cancer risk, and the associations did not vary by these factors (P*interaction* ≥ 0.17).

Discussion

We found no association between choline and betaine intake and colorectal cancer risk in men. Choline intakes from individual sources were also not associated with colorectal cancer risk.

Few epidemiologic studies have examined the association between choline and betaine and cancer risk. We previously found an elevated risk of colorectal adenoma with choline intake (RR=1.45; 95% CI = 1.27-1.67 for top vs. bottom quintile; P*trend*<0.001)(6), but not with betaine intake, and no association between choline or betaine intake and premenopausal breast cancer risk (2). In a nested case-control study of prostate cancer in Sweden, RRs (95% CIs) were 1.36 (0.98-1.88; P*trend* = 0.08) for plasma betaine levels and 1.48 (1.07-2.04; P*trend*= 0.03) for plasma choline levels comparing top with bottom quartiles (3). One case-control study of 1508 breast cancer cases and 1556 controls found an inverse association between choline intake and breast cancer risk; odds ratio (OR) was 0.76 (95% CI = 0.58 –1.00) comparing top quintile with bottom quintile (4).

To our knowledge, this is the first study of choline and betaine intake and colorectal cancer risk. The lack of association may result from choline or betaine intake not being critical in folate-nourished populations, because folate and choline metabolic pathways are highly interrelated (12,13). In the Framingham Offspring Study, we found that the inverse association between choline and betaine intake and homocysteine levels was limited to participants with low folate levels (14). However, in this analysis study, we found no inverse association, even among men with <250 mcg/d of total folate intake.

Our data suggest that choline and betaine intake has little influence on colorectal cancer risk in a population of generally well-nourished men.

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Table 1

Relative risks (RR) and 95% confidence intervals (CIs) of colorectal cancer according to quintiles of energy-adjusted dietary choline and betaine intake in the Health Professionals Follow-up Study

Choline and Betaine*	Quintile of intake					P*trend*
	1	2	3	4	5	
Choline						
Cumulative average						
Age-adjusted RR	1.00	1.00 (0.82-1.23)	0.99 (0.80-1.21)	1.09 (0.89-1.32)	1.00 (0.81-1.22)	0.81
Multivariate RR†	1.00	1.03 (0.84-1.27)	1.01 (0.82-1.24)	1.08 (0.88-1.32)	0.97 (0.79-1.20)	0.87
Baseline						
Multivariate RR†	1.00	0.86 (0.70-1.06)	0.89 (0.72-1.09)	1.02 (0.83-1.24)	0.92 (0.75-1.12)	0.90
0-4 year lag						
Multivariate RR†	1.00	0.90 (0.71-1.14)	1.04 (0.83-1.30)	1.11 (0.89-1.38)	0.96 (0.76-1.19)	0.82
4-8 year lag						
Multivariate RR†	1.00	0.80 (0.61-1.05)	1.04 (0.81-1.34)	1.02 (0.79-1.32)	0.91 (0.71-1.18)	>0.99
8-12 year lag						
Multivariate RR†	1.00	0.83 (0.60-1.14)	0.92 (0.67-1.26)	0.95 (0.70-1.31)	1.08 (0.79-1.47)	0.38
12-16 year lag						
Multivariate RR†	1.00	0.79 (0.52-1.20)	0.78 (0.51-1.19)	0.83 (0.55-1.25)	0.91 (0.60-1.37)	0.76
Betaine						
Cumulative average						
Age-adjusted RR	1.00	0.94 (0.77-1.15)	0.87 (0.71-1.07)	0.97 (0.80-1.18)	0.83 (0.68-1.02)	0.12
Multivariate RR†	1.00	0.99 (0.81-1.21)	0.93 (0.75-1.13)	1.07 (0.88-1.30)	0.94 (0.77-1.16)	0.79
Baseline betaine						
Multivariate RR†	1.00	0.90 (0.74-1.10)	1.04 (0.86-1.27)	0.98 (0.80-1.20)	0.95 (0.78-1.17)	0.82
0-4 year lag						
Multivariate RR†	1.00	1.07 (0.85-1.33)	1.09 (0.87-1.36)	1.14 (0.92-1.43)	1.06 (0.85-1.33)	0.59
4-8 year lag						
Multivariate RR†	1.00	0.69 (0.53-0.90)	0.85 (0.66-1.09)	0.80 (0.62-1.03)	0.92 (0.72-1.18)	0.87
8-12 year lag						

Choline and Betaine*	Quintile of intake					P*trend*
	1	2	3	4	5	
Multivariate RR†	1.00	0.99 (0.72-1.36)	1.20 (0.89-1.64)	1.05 (0.76-1.45)	0.91(0.65-1.27)	0.55
12-16 year lag						
Multivariate RR†	1.00	1.03 (0.68-1.58)	1.36 (0.91-2.04)	1.03 (0.67-1.58)	0.79 (0.49-1.27)	0.25
Choline from individual sources (cumulative average)						
Choline from free choline						
Multivariate RR†	1.00	1.09 (0.88-1.34)	0.99 (0.80-1.23)	0.91 (0.73-1.14)	1.07 (0.86-1.33)	0.98
Choline from glycerophosphocholine						
Multivariate RR†	1.00	1.01 (0.82-1.24)	0.92 (0.75-1.13)	0.95 (0.77-1.17)	0.98 (0.80-1.20)	0.81
Choline from phosphocholine						
Multivariate RR†	1.00	0.83 (0.67-1.02)	0.97 (0.79-1.19)	0.95 (0.77-1.17)	0.97 (0.78-1.19)	0.79
Choline from phosphatidylcholine						
Multivariate RR†	1.00	1.12 (0.91-1.38)	1.00 (0.81-1.23)	1.13 (0.92-1.38)	0.97 (0.79-1.20)	0.70
Choline from sphingomyelin						
Multivariate RR†	1.00	1.05 (0.86-1.29)	1.14 (0.93-1.38)	0.96 (0.78-1.18)	0.99 (0.80-1.21)	0.61

Note: Cumulative average intakes were calculated from all available questionnaires up to the end of each 2-year follow-up interval. For example, choline intake in 1986 was used for analyses of colorectal cancer diagnosed from 1986 through 1990, and the average of choline intake in 1986 and 1990 was used for analyses of colorectal cancer diagnosed from 1990 through 1994. In the baseline analyses, we used only the baseline intake in 1986. We also performed analyses using varying lag times. For example, for latency of 0-4 years before diagnosis, we used choline intake in 1986 for cases diagnosed from 1986 through 1990, intake in 1990 for cases diagnosed from 1990 through 1994, and so forth. For latency of 4-8 years, we used choline intake in 1986 for cases diagnosed from 1990 through 1994, intake in 1990 for cases diagnosed from 1994 through 1998, and so forth. In latency analysis, number of cases differed; 0-4 year lag (n=813 cases), 4-8 year lag (n=614 cases), 8-12 year lag (n=408 cases), and 12-16 year lag (n=233 cases).

*From foods only

†Adjusted for total energy intake (continuous), aspirin dose (never, past, current use 1-2, 3-5, 6-14, ≥15 tablets/wk), pack-years of smoking before age 30 (never smoker, 1-4 years of smoking, 5-10 years, and ≥11 years of smoking), BMI (<23, 23-<25, 25-<30, 30-<35, and ≥35 kg/m^2), family history of colorectal cancer (yes, no), history of endoscopy (yes, no), alcohol intake (never, 0.1-9.9 g/d, 10-14.9 g/d, 15-29.9 g/d, and ≥30 g/d), and total folate (<250, 250-<400, 400-<600, 600-<800, and ≥800 mcg/d).