Higher dietary intakes of choline and betaine are associated with a lower risk of primary liver cancer: a case-control study

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Supplemental Table S1. Top five contributors of food sources of total choline, main choline containing compounds and betaine among all subjects

Nutrients intake	Food source	Proportion (%)
Total choline	Eggs	21.5
(273.5 mg/d)	Streaky Pork	13.0
	Lean Hogs	10.8
	Chinese flowering cabbage, mustard greens, collard greens and broccoli	8.7
	Poultry	4.0
Phosphatidylcholine	Eggs	32.7
(167.9 mg/d)	Streaky Pork	16.1
	Lean Hogs	11.0
	Chinese flowering cabbage, mustard greens, collard greens and broccoli	7.3
	Freshwater fishes	4.4
Sphingomyelin	Streaky Pork	20.9
(13.5 mg/d)	Lean Hogs	18.7
	Eggs	18.1
	Poultry	14.2
	Regular front feet	6.2
Free choline	Chinese flowering cabbage, mustard greens, collard greens and broccoli	10.8
(46.0 mg/d)	Chinese cabbage, cauliflower, celery	8.1
	Chinese cabbage, leaf lettuce, and lettuce	7.6
	Rice	6.9
	Soymilk	5.1
Glycerophosphocholine	Lean Hogs	24.8
(26.7 mg/d)	Rice	15.3
	Streaky Pork	10.6
	Whole milk	9.9
	Porridge	5.7
Phosphocholine	Chinese flowering cabbage, mustard greens, collard greens and broccoli	40.5
(13.1 mg/d)	Chinese cabbage, leaf lettuce, and lettuce	6.5
	Whole milk	4.9
	Wax gourd, cucumber and zucchini	4.8
	Soymilk	4.7
Betaine	Noodles	26.1
(85.4 mg/d)	Spinach	23.4
	Steamed buns	14.9
	Whole-wheat bread	9.5
	Freshwater fishes	6.0

Methionine	Rice	34.4
(1904 mg/d)	Porridge	12.9
	Lean hogs	10.9
	Freshwater fishes	5.5
	Eggs	4.4

Supplemental Table S2. Associations between tertiles of total choline, betaine, methionine intake and primary liver cancer risk according to lifestyle behaviors[1]

	n (cases/controls)	OR (95% CI)	n (cases/controls)	OR (95% CI)
Smoking	**No**		**Yes**	
Tertile of total choline				
T1	161/120	1.00	155/94	1.00
T2	78/121	0.48 (0.32, 0.73)	104/95	0.64 (0.42, 0.97)
T3	60/120	0.38 (0.25, 0.59)	86/94	0.47 (0.30, 0.72)
P-trend		<0.001		0.001
P-interaction		0.406		
Tertile of betaine				
T1	133/120	1.00	171/94	1.00
T2	90/121	0.84 (0.56, 1.27)	79/95	0.48 (0.31, 0.73)
T3	76/120	0.76 (0.50, 1.16)	95/94	0.54 (0.35, 0.83)
P-trend		0.199		0.003
P-interaction		0.259		
Tertile of methionine				
T1	81/120	1.00	99/94	1.00
T2	68/121	0.77 (0.49, 1.20)	96/95	1.01 (0.65, 1.55)
T3	150/120	1.65 (1.10, 2.47)	150/94	1.25 (0.83, 1.90)
P-trend		0.008		0.276
P-interaction		0.218		
Score *				
0	62/27	1.00	70/32	1.00
1	116/112	0.39 (0.22, 0.71)	145/81	0.72 (0.42, 1.24)
2	86/136	0.26 (0.14, 0.47)	105/124	0.34 (0.20, 0.59)
3	35/86	0.19 (0.10, 0.38)	25/46	0.23 (0.11, 0.48)
P-trend		<0.001		<0.001
P-interaction		0.790		
Alcohol use	**No**		**Yes**	
Tertile of total choline				
T1	210/173	1.00	127/41	1.00
T2	132/173	0.63 (0.45, 0.87)	42/42	0.34 (0.18, 0.62)
T3	94/173	0.45 (0.32, 0.65)	39/42	0.31 (0.17, 0.57)
P-trend		<0.001		<0.001
P-interaction		0.070		
Tertile of betaine				
T1	207/173	1.00	94/41	1.00
T2	114/173	0.62 (0.44, 0.86)	70/42	0.82 (0.46, 1.47)
T3	115/173	0.61 (0.44, 0.87)	44/42	0.55 (0.30, 1.03)
P-trend		0.004		0.064
P-interaction		0.918		

Tertile of methionine				
T1	117/173	1.00	68/41	1.00
T2	108/173	0.93 (0.65, 1.32)	61/42	0.91 (0.49, 1.68)
T3	211/173	1.73 (1.24, 2.42)	79/42	1.04 (0.58, 1.86)
P-trend		0.001		0.894
P-interaction		0.179		
Score				
0	93/45	1.00	39/14	1.00
1	176/167	0.44 (0.28, 0.69)	85/26	1.12 (0.50, 2.49)
2	127/210	0.26 (0.16, 0.41)	64/50	0.48 (0.22, 1.04)
3	40/97	0.20 (0.11, 0.36)	20/35	0.26 (0.10, 0.63)
P-trend		<0.001		<0.001
P-interaction		0.669		
Drink tea		**No**		**Yes**
Tertile of total choline				
T1	139/82	1.00	176/132	1.00
T2	80/82	0.56 (0.36, 0.89)	115/133	0.62 (0.43, 0.90)
T3	72/82	0.42 (0.26, 0.67)	62/133	0.35 (0.23, 0.54)
P-trend		<0.001		<0.001
P-interaction		0.360		
Tertile of betaine				
T1	115/82	1.00	167/132	1.00
T2	97/82	0.88 (0.56, 1.37)	97/133	0.80 (0.54, 1.17)
T3	79/82	0.64 (0.41, 1.02)	89/133	0.66 (0.44, 0.98)
P-trend		0.062		0.038
P-interaction		0.399		
Tertile of methionine				
T1	76/82	1.00	106/132	1.00
T2	71/82	0.96 (0.60, 1.55)	90/133	0.75 (0.50, 1.13)
T3	144/82	1.96 (1.25, 3.06)	157/133	1.16 (0.79, 1.71)
P-trend		0.002		0.385
P-interaction		0.401		
Score				
0	63/28	1.00	69/31	1.00
1	127/91	0.52 (0.29, 0.92)	134/102	0.57 (0.33, 0.99)
2	79/92	0.31 (0.17, 0.57)	112/168	0.30 (0.17, 0.51)
3	22/35	0.18 (0.08, 0.40)	38/97	0.23 (0.12, 0.43)
P-trend		<0.001		<0.001
P-interaction		0.686		
BMI(kg/m$^{2)}$		**<25**		**⩾25**
Tertile of total choline				
T1		1.00		1.00
T2	252/157	0.58 (0.41, 0.80)	69/57	0.51 (0.28, 0.91)

T3	141/157	0.39 (0.27, 0.56)	43/58	0.37 (0.20, 0.70)
P-trend	107/157	<0.001	32/58	0.002
P-interaction		0.929		
Tertile of betaine				
T1	247/157	1.00	54/57	1.00
T2	131/157	0.61 (0.44, 0.85)	46/58	0.94 (0.52, 1.71)
T3	122/157	0.51 (0.36, 0.73)	44/58	1.03 (0.57, 1.88)
P-trend		<0.001		0.920
P-interaction		0.044		
Tertile of methionine				
T1	150/157	1.00	40/57	1.00
T2	119/157	0.82 (0.58, 1.17)	27/58	0.77 (0.40, 1.48)
T3	231/157	1.47 (1.06, 2.03)	77/58	1.80 (1.00, 3.23)
P-trend		0.016		0.034
P-interaction		0.547		
Score				
0	106/41	1.00	26/18	1.00
1	205/140	0.52 (0.33, 0.81)	56/53	0.73 (0.33, 1.63)
2	145/195	0.27 (0.17, 0.43)	46/65	0.49 (0.22, 1.08)
3	44/95	0.19 (0.11, 0.33)	16/37	0.35 (0.14, 0.88)
P-trend		<0.001		0.009
P-interaction		0.228		
Age (years)		**≤54**		**>54**
Tertile of total choline				
T1	161/108	1.00	166/106	1.00
T2	98/109	0.55 (0.37, 0.82)	79/107	0.53 (0.34, 0.82)
T3	66/108	0.31 (0.20, 0.49)	74/106	0.51 (0.33, 0.80)
P-trend		<0.001		0.002
P-interaction		0.486		
Tertile of betaine				
T1	119/108	1.00	181/106	1.00
T2	101/109	0.82 (0.55, 1.24)	64/107	0.46 (0.29, 0.71)
T3	105/108	0.88 (0.58, 1.32)	74/106	0.49 (0.32, 0.76)
P-trend		0.541		0.001
P-interaction		0.019		
Tertile of methionine				
T1	124/108	1.00	65/106	1.00
T2	76/109	0.61 (0.40, 0.92)	69/107	0.95 (0.58, 1.55)
T3	125/108	0.93 (0.63, 1.37)	185/106	2.74 (1.75, 4.28)
P-trend		0.707		<0.001
P-interaction		<0.001		
Score				
0	68/40	1.00	64/19	1.00

1	136/109	0.71 (0.43, 1.17)	125/84	0.39 (0.20, 0.75)
2	95/131	0.39 (0.23, 0.65)	96/129	0.22 (0.11, 0.42)
3	26/45	0.29 (0.15, 0.57)	34/87	0.15 (0.07, 0.31)
P-trend		<0.001		<0.001
P-interaction		0.155		
Physical activity (MET· h per day)		**≤33.3**		**>33.3**
Tertile of total choline				
T1	210/71	1.00	125/143	1.00
T2	127/72	0.45 (0.27, 0.75)	57/143	0.50 (0.32, 0.77)
T3	92/72	0.42 (0.24, 0.73)	33/143	0.27 (0.16, 0.44)
P-trend		0.001		<0.001
P-interaction		0.047		
Tertile of betaine				
T1	192/71	1.00	112/143	1.00
T2	122/72	0.94 (0.56, 1.56)	55/143	0.61 (0.40, 0.95)
T3	115/72	0.88 (0.52, 1.51)	48/143	0.51 (0.32, 0.80)
P-trend		0.643		0.003
P-interaction		0.225		
Tertile of methionine				
T1	109/71	1.00	69/143	1.00
T2	102/72	0.93 (0.54, 1.62)	53/143	0.79 (0.50, 1.25)
T3	218/72	1.52 (0.90, 2.54)	93/143	1.28 (0.84, 1.97)
P-trend		0.091		0.225
P-interaction		0.245		
Score				
0	81/11	1.00	51/48	1.00
1	167/67	0.31 (0.14, 0.70)	94/126	0.76 (0.45, 1.27)
2	138/91	0.22 (0.10, 0.51)	53/169	0.36 (0.21, 0.62)
3	43/46	0.16 (0.07, 0.41)	17/86	0.25 (0.12, 0.51)
P-trend		<0.001		<0.001
P-interaction		0.831		
Education level		**Low**		**High**
Tertile of total choline				
T1	178/87	1.00	138/127	1.00
T2	105/87	0.54 (0.35, 0.83)	87/128	0.53 (0.35, 0.81)
T3	66/87	0.31 (0.20, 0.49)	70/128	0.42 (0.27, 0.66)
P-trend		<0.001		<0.001
P-interaction		0.327		
Tertile of betaine				
T1	161/87	1.00	130/127	1.00
T2	96/87	0.65 (0.43, 1.01)	81/128	0.75 (0.49, 1.13)
T3	92/87	0.56 (0.36, 0.86)	84/128	0.78 (0.51, 1.18)

P-trend		0.008		0.216
P-interaction		0.359		
Tertile of methionine				
T1	116/87	1.00	74/127	1.00
T2	80/87	0.64 (0.41, 0.99)	73/128	0.98 (0.62, 1.53)
T3	153/87	1.16 (0.77, 1.76)	148/128	1.79 (1.17, 2.72)
P-trend		0.429		0.004
P-interaction		0.139		
Score				
0	84/32	1.00	48/27	1.00
1	157/101	0.55 (0.33, 0.93)	104/92	0.64 (0.34, 1.20)
2	89/100	0.31 (0.18, 0.53)	102/160	0.38 (0.20, 0.69)
3	19/28	0.21 (0.09, 0.46)	41/104	0.25 (0.13, 0.50)
P-trend		<0.001		<0.001
P-interaction		0.702		
HBV infectious	**No**		**Yes**	
Tertile of total choline				
T1	61/214	1.00	266/214	1.00
T2	29/215	0.47 (0.27, 0.80)	148/215	0.53 (0.39, 0.72)
T3	31/215	0.37 (0.21, 0.64)	109/215	0.37 (0.27, 0.52)
P-trend		<0.001		<0.001
Tertile of betaine				
T1	63/214	1.00	239/214	1.00
T2	32/215	0.55 (0.33, 0.92)	141/215	0.68 (0.50, 0.92)
T3	26/215	0.42 (0.24, 0.73)	143/215	0.66 (0.48, 0.89)
P-trend		0.002		0.006
Tertile of methionine				
T1	35/214	1.00	148/214	1.00
T2	26/215	0.72 (0.40, 1.30)	136/215	0.91 (0.66, 1.25)
T3	60/215	1.43 (0.86, 2.38)	239/215	1.55 (1.14, 2.09)
P-trend		0.128		0.003
Score				
0	29/59	1.00	103/59	1.00
1	48/193	0.48 (0.26, 0.90)	213/193	0.59 (0.39, 0.89)
2	33/260	0.23 (0.12, 0.45)	158/260	0.33 (0.22, 0.49)
3	11/132	0.17 (0.07, 0.40)	49/132	0.22 (0.13, 0.36)
P-trend		<0.001		<0.001
Diagnosis	**Tissue evaluation**		**MRI imaging**	
Tertile of total choline				
T1	124/214	1.00	203/214	1.00
T2	57/215	0.43 (0.28, 0.64)	120/215	0.60 (0.43, 0.83)
T3	46/215	0.33 (0.21, 0.51)	94/215	0.41 (0.29, 0.58)
P-trend		<0.001		<0.001

Tertile of betaine				
T1	112/214	1.00	190/214	1.00
T2	69/215	0.71 (0.48, 1.04)	104/215	0.63 (0.45, 0.88)
T3	46/215	0.46 (0.30, 0.70)	123/215	0.71 (0.51, 0.99)
P-trend		<0.001		0.032
Tertile of methionine				
T1	62/214	1.00	121/214	1.00
T2	72/215	1.15 (0.76, 1.74)	90/215	0.72 (0.50, 1.02)
T3	93/215	1.36 (0.91, 2.04)	206/215	1.54 (1.12, 2.13)
P-trend		0.135		0.004
Score				
0	47/59	1.00	85/59	1.00
1	96/193	0.54 (0.33, 0.91)	165/193	0.55 (0.36, 0.85)
2	65/260	0.28 (0.16, 0.47)	126/260	0.32 (0.21, 0.49)
3	19/132	0.17 (0.09, 0.34)	41/132	0.22 (0.13, 0.38)
P-trend		<0.001		<0.001

ORs (95% CI): from multivariate unconditional logistic regression models.

[1]adjusted for sex, age, daily energy intake (ln-transformed), BMI, education level, occupation, household income, smoking, alcohol consumption, drink tea, physical activity.

P-trend: α for p-trends = 0.05/6(tests) = 0.0083

Abbreviation: CI=confidence interval

*: summing the scores of each nutrient of choline (0= < median, 1= ≥ median), betaine (0= < median, 1= ≥ median), and methionine (0 = quartile 1 and 4, 1= quartile 2 and 3)

Supplemental Table S 3 . Odds ratios (OR) and 95% confidence intervals (CI) of primary liver cancer according to tertiles of total choline, betaine, methionine intake in men

	Amount (mg/d)	**n (cases/controls)**	**Model1 OR (95% CI)**	**Model2 OR (95% CI)**
Tertile of choline				
T1	<253	269/186	1.00	1.00
T2	253-315	161/186	0.61 (0.46, 0.81)	0.59 (0.44, 0.80)
T3	>315	129/187	0.48 (0.36, 0.64)	0.44 (0.32, 0.62)
P-trend			<0.001	<0.001
Tertile of betaine				
T1	<72	259/186	1.00	1.00
T2	72-117	149/186	0.57 (0.42, 0.75)	0.64 (0.47, 0.87)
T3	>117	151/187	0.57 (0.43, 0.76)	0.64 (0.47, 0.88)
P-trend			<0.001	0.005
Tertile of methionine				
T1	<1757	169/186	1.00	1.00
T2	1757-2004	136/186	0.81 (0.60, 1.10)	0.92 (0.66, 1.28)

T3	>2004	254/187	1.51 (1.14, 2.00)	1.71 (1.22, 2.39)
P-trend			0.002	0.001
Tertile of folate（μg/d）				
T1	<309	199/186	1.00	1.00
T2	309-360	160/186	0.81 (0.60, 1.09)	1.31 (0.91, 1.89)
T3	>360	200/187	1.02 (0.76, 1.35)	2.66 (1.57, 4.51)
P-trend			0.915	<0.001

Models 1 and 2: from conditional logistic model.

Model 1: adjusted for daily energy intake (ln-transformed), besides matched by sex and age.

Model 2: Model 1 +, BMI, education level, occupation, household income, smoking, drinking, drink tea, physical activity and dietary folate intake.