Dietary N-Nitroso Compounds and Risk of Hepatocellular Carcinoma: A US-Based Study

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Author contributions

J.Z. and M.H. designed the study and drafted the manuscript. J.Z. conducted the analyses. J.Z., J.S., C.R.D., D.L., and M.M.H. contributed to the design of the analyses and interpretation of results. J.S. designed the N-nitroso compound concentration database. D.L. and R.I.H. contributed to dietary data collection, management and initial data cleaning. D.L. contributed to control recruitment. A.O.K., P.K.J., and Y.S.C contributed to patient recruitment. R.I.H interviewed cancer patients for all the environmental factors and contacted patients for retrieving the diet questionnaires. A.R.

contributed to the pathological definition of cirrhosis, and virus testing. A.A.A reviewed the radiology and pathology reports of patients for evidence of cirrhosis. All authors critically reviewed, revised, and approved the manuscript.

Supplemental Table 1. Multivariable-adjusted odds ratios and 95% CIs of HCC risk according to quartiles of consumption of other N-Nitroso compounds (mcg per 1000 kcal/day)

N-nitroso compounds from dietary sources	Quartiles of intake [a]				*P*-trend [b]
	Q1	Q2	Q3	Q4	
N-Methyl-N-ethylnitrosamine (NMEA)					
Mean (range)	0.0006 (<0.001-0.001)	0.001 (0.0008-0.0014)	0.0015 (0.001-0.002)	0.002 (0.001-0.006)	
Case/control (n)	201/254	151/253	225/253	250/253	
Multivariable-adjusted OR (95% CI) [c]	1.00	0.55 (0.35-0.86)	1.09 (0.73-1.65)	0.88 (0.58-1.35)	0.86
Plant sources					
Case/control (n)	199/254	153/253	210/253	265/253	
Multivariable-adjusted OR (95% CI) [d]	1.00	0.65 (0.42-1.01)	0.87 (0.57-1.33)	0.91 (0.60-1.40)	0.70
Animal sources					
Case/control (n)	209/254	313/322	157/184	148/253	
Multivariable-adjusted OR (95% CI) [e]	1.00	1.09 (0.70-1.70)	1.42 (0.87-2.32)	0.83 (0.51-1.36)	0.40
N-nitrosodibenzylamine (NDBZA)[f]					
Mean (range)	0	0.07 (0.02-0.09)	0.11 (0.06-0.15)	0.34 (0.10-2.48)	
Case/control (n)	329/288	79/219	151/253	268/253	
Multivariable-adjusted OR (95% CI) [c,e]	1.00	0.19 (0.11-0.33)	0.53 (0.35-0.81)	**0.59 (0.39-0.88)**	*
N-nitroso-2-(hydroxymethyl)thiazolidine (NHMT)[f]					
Mean (range)	0.0002 (<0.001-0.0014)	0.002 (0.0005-0.0025)	0.002 (0.0018-0.004)	0.01 (0.003-0.09)	
Case/control (n)	268/276	149/231	126/253	284/253	
Multivariable-adjusted OR (95%CI) [c,e]	1.00	0.68 (0.43-1.07)	0.38 (0.24-0.60)	0.92 (0.62-1.37)	*
N-nitroso-2-hydroxymethylthiazolidine-4-carboxylic acid (NHMTCA) [f]					
Mean (range)	4.78 (<0.001-11.43)	16.23 (9.55-31.09)	30.55 (19.71-52.51)	90.39 (37.22-596.51)	
Case/control (n)	260/254	230/253	155/253	182/253	
Multivariable-adjusted OR (95% CI) [c,e]	1.00	1.00 (0.66-1.50)	0.85 (0.54-1.33)	0.83 (0.53-1.31)	0.39
N- nitroso-4-hydroxyproline (NHPRO)[f]					
Mean (range)	0.01 (<0.001-0.06)	0.12 (0.04-0.18)	0.22 (0.13-0.30)	0.65 (0.24-4.14)	
Case/control (n)	240/254	139/253	184/253	264/253	
Multivariable-adjusted OR (95% CI) [c,e]	1.00	0.60 (0.38-0.96)	0.84 (0.54-1.29)	0.76 (0.49-1.16)	0.13

N-nitrosomorpholine (NMOR)					
Mean (range)	0.001 (<0.001-0.003)	0.0034 (0.002-0.004)	0.005 (0.004-0.007)	0.01 (0.006-0.074)	
Case/control (n)	266/254	132/253	141/253	**288/253**	
Multivariable-adjusted OR (95% CI) [c]	1.00	0.57 (0.37-0.89)	0.58 (0.38-0.91)	0.79 (0.52-1.18)	*
Plant sources					
Case/control (n)	410/345	47/169	101/246	**269/253**	
Multivariable-adjusted OR (95% CI) [d]	1.00	0.15 (0.08-0.29)	0.18 (0.11-0.29)	**0.64 (0.44-0.92)**	*
Animal sources					
Case/control (n)	244/254	150/253	157/253	276/253	
Multivariable-adjusted OR (95% CI) [e]	1.00	0.75 (0.48-1.17)	0.86 (0.55-1.34)	0.87 (0.57-1.33)	0.49
N-nitroso-5-methyloxazolidine-4-carboxylic acid (NMOCA)[f]					
Mean (range)	0	0.016 (0.005-0.02)	0.024 (0.014-0.034)	0.078 (0.024-0.57)	
Case/control (n)	329/288	79/219	151/253	268/253	
Multivariable-adjusted OR (95% CI) [c,e]	1.00	0.19 (0.11-0.33)	0.53 (0.35-0.81)	**0.59 (0.39-0.88)**	*
N-nitroso-2-methylthiazolidine-4-carboxylic acid (NMTCA)[f]					
Mean (range)	0.004 (0.0001-0.016)	0.028 (0.013-0.039)	0.049 (0.029-0.069)	0.15 (0.06-0.82)	
Case/control (n)	239/254	129/253	223/253	236/253	
Multivariable-adjusted OR (95% CI) [c,e]	1.00	0.59 (0.37-0.94)	1.05 (0.69-1.60)	**0.63 (0.40-0.97)**	**0.10**
N-nitrososarcosine (NSAR)[f]					
Mean (range)	0	0.005 (0.002-0.006)	0.007 (0.004-0.01)	0.02 (0.01-0.17)	
Case/control (n)	329/288	79/219	151/253	268/253	
Multivariable-adjusted OR (95% CI) [c,e]	1.00	0.19 (0.11-0.33)	0.53 (0.34-0.81)	**0.59 (0.39-0.88)**	*
N-nitrosothiazolidine carboxylic acid and related homologues (NTHZCA)[f]					
Mean (range)	0	0.23 (0.18-0.26)	0.37 (0.13-0.71)	1.32 (0.44-13.36)	
Case/control (n)	347/505	15/4	233/251	232/253	
Multivariable-adjusted OR (95% CI) [c,e]	1.00	11.83 (1.46-95.94)	1.40 (0.95-2.07)	1.00 (0.68-1.47)	0.33
N-nitrosoproline (NPRO)					
Mean (range)	3.27 (0.0001-5.06)	6.13 (4.77-8.38)	8.94 (7.05-12.46)	16.40 (10.15-56.30)	
Case/control (n)	247/254	224/253	161/253	195/253	

Multivariable-adjusted OR (95% CI) [c]	1.00	1.15 (0.77-1.74)	0.71 (0.46-1.10)	0.82 (0.53-1.27)	0.21
Plant sources					
Case/control (n)	257/254	212/253	156/253	202/253	
Multivariable-adjusted OR (95% CI) [d]	1.00	0.89 (0.59-1.34)	0.65 (0.42-1.01)	0.70 (0.45-1.09)	0.06
Animal sources					
Case/control (n)	178/254	131/253	275/253	243/253	
Multivariable-adjusted OR (95% CI) [e]	1.00	0.97 (0.61-1.55)	1.34 (0.87-2.05)	1.08 (0.70-1.68)	0.48
N-nitrosothiazolidine-4 carboxylic-acid (NTCA)[f]					
Mean (range)	2.09 (0.0001-3.35)	3.53 (2.97-4.10)	4.84 (4.00-5.74)	9.26 (5.51-50.30)	
Case/control (n)	235/254	118/253	179/253	295/253	
Multivariable-adjusted OR (95% CI) [c,e]	1.00	0.52 (0.33-0.83)	0.79 (0.51-1.21)	1.04 (0.69-1.56)	*
N-nitrosothiazolidine (NTHZ)[f]					
Mean (range)	0.08 (0.0001-0.14)	0.16 (0.13-0.20)	0.24 (0.19-0.29)	0.40 (0.28-1.20)	
Case/control (n)	285/254	163/253	201/253	178/253	
Multivariable-adjusted OR (95% CI) [c,e]	1.00	0.59 (0.39-0.91)	0.63 (0.41-0.96)	**0.49 (0.32-0.76)**	**0.001**

a. Quartile cut-off points were set as the energy-adjusted log-transformed FFQ-specific value based on control's distribution
b. P-trend was calculated by using the median value of each quartile of NOC consumption as a continuous variable in the multivariable-adjusted model. P-trend was noted as "*", If the linearity assumption was not met after assessing it with the restricted cubic spline function within the logistic model ($P_{non\text{-}linearity}<0.05$).
c. The model was adjusted for total calorie, age, sex, race, education level, BMI status, alcohol level, and history of diabetes, smoking status, family history of liver cancer, HCV and HBV status as categorized in Table 1.
d. Multivariable-adjusted model for N-nitroso compounds from plant sources was additionally adjusted for red and processed meet intake level (classified as four-level categorical)
e. Multivariable-adjusted model for N-nitroso compounds from animal sources was additionally adjusted for total vegetable and fruit intake level (classified as four-level categorical)
f. Total N-nitroso compounds consumption were all from animal sources

Supplemental Table 2. Top 5 food contributors* to NOCs, nitrite and nitrate and energy-adjusted correlation coefficients by case status

Compounds	1	2	3	4	5
Total NOC					
Case	Green leafy vegetables (ρ=0.89)	Other vegetables [a] (ρ=0.52)	Roots[b] (ρ=0.38)	Fresh seafood[c] (ρ=0.23)	Chicken (ρ=0.18)
Control	Green leafy vegetables (ρ=0.89)	Other vegetables [a] (ρ=0.44)	Roots[b] (ρ=0.26)	Chicken (ρ=0.22)	Fresh seafood[c] (ρ=0.21)
Plant sources					
Case	Green leafy vegetables (ρ=0.90)	Other vegetables [a] (ρ=0.53)	Roots[b] (ρ=0.37)	Liquid oil[d] (ρ=0.18)	Tofu (ρ=0.13)
Control	Green leafy vegetables (ρ=0.90)	Other vegetables [a] (ρ=0.45)	Roots[b] (ρ=0.26)	Beans and pulses (ρ=0.17)	Tofu (ρ=0.12)
Animal sources					
Case	Beef (ρ=0.65)	Cured lunch meats [e] (ρ=0.48)	Bacon (ρ=0.38)	Sausage (ρ=0.37)	Chicken (ρ=0.32)
Control	Beef (ρ=0.70)	Chicken (ρ=0.39)	Cured lunch meats[e] (ρ=0.35)	Bacon (ρ=0.25)	Egg (ρ=0.18)
NDEA					
Case	Fresh seafood [c] (ρ=0.44)	Other grains [f] (ρ=0.43)	Fermented cheese[g] (ρ=0.34)	Salmon (ρ=0.30)	Cured lunch meats[e] (ρ=0.25)
Control	Other grains [f] (ρ=0.53)	Fermented cheese [g] (ρ=0.47)	Fresh seafood[c] (ρ=0.44)	Salmon (ρ=0.27)	Green leafy vegetables (ρ=0.20)
Plant sources					
Case	Other grains [f] (ρ=0.99)	Tofu (ρ=0.18)	Other vegetables[a] (ρ=0.14)	Beans and pulses (ρ=0.14)	Green leafy vegetables (ρ=0.13)
Control	Other grains [f] (ρ=0.99)	Other vegetables [a] (ρ=0.12)	Tofu (ρ=0.10)	Beans and pulses (ρ=0.09)	Green leafy vegetables (ρ=0.08)
Animal sources					
Case	Fermented cheese [g] (ρ=0.47)	Fresh seafood [c] (ρ=0.46)	Cured lunch meats[e] (ρ=0.39)	Cooked meat[h] (ρ=0.34)	Salmon (ρ=0.28)
Control	Fermented cheese [g] (ρ=0.55)	Fresh seafood [c] (ρ=0.48)	Cured lunch meats[e] (ρ=0.31)	Salmon (ρ=0.31)	Cooked meat[h] (ρ=0.11)
NDMA					
Case	Sausage	Pizza	Cooked meat	Beer	Organ meats

	(ρ=0.71)	(ρ=0.48)	(ρ=0.32)	(ρ=0.27)	(ρ=0.26)
Control	Pizza (ρ=0.66)	Beer (ρ=0.45)	Salmon (ρ=0.26)	Sausage (ρ=0.20)	Liquor (ρ=0.17)
Plant sources					
Case	Other grains[f] (ρ=0.97)	Roots [b] (ρ=0.19)	Beans and pulses (ρ=0.14)	Other vegetables[a] (ρ=0.13)	Tofu (ρ=0.13)
Control	Other grains[f] (ρ=0.98)	Other vegetables [a] (ρ=0.12)	Beans and pulses (ρ=0.12)	Roots[b] (ρ=0.11)	Green leafy vegetables (ρ=0.08)
Animal sources					
Case	Sausage (ρ=0.74)	Pizza (ρ=0.53)	Cooked meat[h] (ρ=0.36)	Organ meats (ρ=0.32)	Hot dog (ρ=0.27)
Control	Pizza (ρ=0.83)	Salmon (ρ=0.29)	Sausage (ρ=0.22)	Fresh seafood (ρ=0.19)	Hot dog (ρ=0.19)
Nitrate (NO_3)					
Case	Green leafy vegetables (ρ=0.90)	Other vegetables [a] (ρ=0.52)	Roots[b] (ρ=0.38)	Fresh seafood (ρ=0.23)	Chicken (ρ=0.18)
Control	Green leafy vegetables (ρ=0.90)	Other vegetables [a] (ρ=0.44)	Roots[b] (ρ=0.26)	Chicken (ρ=0.22)	Fresh seafood (ρ=0.21)
Plant sources					
Case	Green leafy vegetables (ρ=0.90)	Other vegetables (ρ=0.53)	Roots[b] (ρ=0.38)	Liquid oil[d] (ρ=0.18)	Tofu (ρ=0.13)
Control	Green leafy vegetables (ρ=0.90)	Other vegetables (ρ=0.45)	Roots[b] (ρ=0.26)	Beans and pulses (ρ=0.17)	Tofu (ρ=0.12)
Animal sources					
Case	Beef (ρ=0.58)	Cured lunch meats [e] (ρ=0.45)	Sausage (ρ=0.40)	Chicken (ρ=0.40)	Bacon (ρ=0.36)
Control	Beef (ρ=0.55)	Chicken (ρ=0.55)	Cured lunch meats[e] (ρ=0.28)	Bacon (ρ=0.21)	Pizza (ρ=0.19)
Nitrite (NO_2)[i]					
Case	Beef (ρ=0.78)	Cured lunch meats [e] (ρ=0.50)	Hot dog (ρ=0.43)	Bacon (ρ=0.38)	Sausage (ρ=0.22)
Control	Beef (ρ=0.90)	Cured lunch meats [e] (ρ=0.45)	Hot dog (ρ=0.32)	Bacon (ρ=0.30)	Egg (ρ=0.18)
NDBA[i]					
Case	Beef	Cured lunch meats [e]	Bacon		

	(ρ=0.99)	(ρ=0.34)	(ρ=0.26)		
Control	Beef (ρ=0.99)	Cured lunch meats [e] (ρ=0.27)	Bacon (ρ=0.17)		
NDPA[i]					
Case	Fermented cheese [g] (ρ=0.87)	Fresh seafood (ρ=0.44)	Salmon (ρ=0.15)	Cooked meat[h] (ρ=0.10)	
Control	Fermented cheese [g] (ρ=0.89)	Fresh seafood (ρ=0.44)	Salmon (ρ=0.18)		
NPIP[i]					
Case	Cured lunch meats[e] (ρ=0.55)	Fresh dairy [j] (ρ=0.43)	Fermented cheese [g] (ρ=0.27)	Cooked meat[h] (ρ=0.18)	Bacon (ρ=0.16)
Control	Cured lunch meats[e] (ρ=0.53)	Fresh dairy [j] (ρ=0.39)	Fermented cheese [g] (ρ=0.35)	Bacon (ρ=0.18)	Evaporated diary products[k] (ρ=0.18)
NMAMBA					
Case	Other grains [f,l] (ρ=0.98)	Pizza (ρ=0.08)			
Control	Other grain [f,m] (ρ=0.99)	Pizza (ρ=0.13)			
Plant sources					
Case	Other grains [f,l] (ρ=0.99)				
Control	Other grains [f,m] (ρ=1.00)				
Animal sources					
Case	Pizza (ρ=1.00)				
Control	Pizza (ρ=1.00)				
NPYR					
Case	Bacon (ρ=0.55)	Chicken (ρ=0.37)	Egg (ρ=0.33)	Cured lunch meats [e] (ρ=0.24)	Roots [b] (ρ=0.24)
Control	Chicken (ρ=0.53)	Wine (ρ=0.41)	Bacon (ρ=0.36)	Egg (ρ=0.25)	Fresh seafood[c] (ρ=0.19)
Plant sources					

Case	Other vegetables [a] (ρ=0.64)	Roots [b] (ρ=0.47)	Other grains [f] (ρ=0.39)	Tofu (ρ=0.28)	
Control	Other vegetables [a] (ρ=0.57)	Roots [b] (ρ=0.44)	Other grains [f] (ρ=0.43)	Tofu (ρ=0.21)	
Animal sources					
Case	Bacon (ρ=0.67)	Chicken (ρ=0.40)	Cured lunch meats [e] (ρ=0.34)	Egg (ρ=0.33)	Cooked meat (ρ=0.20)
Control	Chicken (ρ=0.61)	Bacon (ρ=0.53)	Egg (ρ=0.34)	Cured lunch meats [e] (ρ=0.27)	Fresh seafood [c] (ρ=0.09)

*Energy-adjusted correlation coefficient between each food group contributing to NOC and NOC was calculated to rank the top 5 food contributors if applicable using spearmen correlation method. For each NOC, the top 5 food group contributors for case and control separately were listed in order in this table. All correlation coefficients in this table have P values<0.05.

a. Other vegetables refer to those non-green leafy vegetables such as zucchini and carrots
b. Roots include yams, potato or potato products in the study
c. Fresh seafood includes shrimp, other fishes and tuna in this study
d. Liquid oil refers to olive oil in the study
e. Cured lunch meats include cured/processed lunch meats such as salami and kielbasa and others
f. Other grains in this study include brown rice, white rice, chocolate chip, farina (creamed wheat), cookies and bars, oatmeal, bran flakes (breakfast cereal), rye bread, dark bread, muffins, pancake, pasta, popcorn, rolls or sweet rolls.
g. Fermented cheese in this study include cottage cheese, cream cheese, American cheese, sour cream, and yogurt
h. Cooked meat refers to pork.
i. Total N-nitroso compounds consumption were all from animal sources.
j. Fresh diary includes skim milk, whole milk, 2% and 1% milk and ice cream, sherbet in the study
k. Evaporated dairy products are cream, coffee whitener and butter
l. Top five food items in this category that contribute to NMAMBA are cooked oatmeal/cooked oat bran, other cooked breakfast cereal, brown rice, English muffin, and white rice
m. Top five food items in this category that contribute to NMAMBA are cooked oatmeal/cooked oat bran, other cooked breakfast cereal, brown rice, English muffin, dark/whole wheat bread

Supplemental Table 3. Multivariable-adjusted odds ratios and 95% CIs of HCC according to quartiles of consumption of major food contributors to NDEA, NDMA, NMAMBA and NPIP (mcg per 1000 kcal/day)

Major food contributors	Quartiles of intake[a]				P-trend[b]
	Q1	Q2	Q3	Q4	
Major plant-based food contributors to NDEA, NDMA and NMAMBA					
Grains[c]					
Case/control (n)	170/254	136/253	208/253	313/253	
Multivariable-adjusted OR (95% CI)[d]	1.00	0.82 (0.52-1.29)	0.98 (0.63-1.52)	1.60 (1.04-2.45)	0.03
Non-green leafy vegetables					
Case/control (n)	261/254	213/253	155/253	198/253	
Multivariable-adjusted OR (95% CI)[d]	1.00	0.85 (0.56-1.28)	0.65 (0.42-1.00)	0.72 (0.47-1.11)	0.03
Tofu[e]					
Case/control (n)	731/908			96/105	
Multivariable-adjusted OR (95% CI)[d]	1.00			1.01 (0.60-1.71)	0.97
Roots					
Case/control (n)	278/254	156/253	162/253	231/253	
Multivariable-adjusted OR (95% CI)[d]	1.00	0.80 (0.52-1.23)	0.82 (0.54-1.25)	1.28 (0.85-1.94)	0.07
Green leafy vegetables					
Case/control (n)	271/254	178/253	161/253	217/253	
Multivariable-adjusted OR (95% CI)[d]	1.00	0.68 (0.44-1.04)	0.73 (0.47-1.13)	0.83 (0.55-1.26)	*
Major non-plant food contributors to NDEA, NDMA and NMAMBA[f]					
Fermented cheese products					
Case/control (n)	274/254	217/253	155/253	181/253	
Multivariable-adjusted OR (95% CI)[d]	1.00	0.93 (0.62-1.40)	0.85 (0.55-1.33)	0.83 (0.54-1.29)	0.88
Fresh seafood					
Case/control (n)	207/254	182/253	190/253	248/253	
Multivariable-adjusted OR (95% CI)[d]	1.00	1.13 (0.73-1.76)	1.02 (0.66-1.57)	1.25 (0.82-1.92)	*
Cured lunch meats					
Case/control (n)	329/288	79/219	151/253	268/253	
Multivariable-adjusted OR (95% CI)[d]	1.00	0.19 (0.11-0.34)	0.51 (0.34-0.78)	0.63 (0.42-0.93)	<.0001
Pizza					
Case/control (n)	280/294	198/213	201/253	148/253	
Multivariable-adjusted OR (95% CI)[d]	1.00	1.11 (0.69-1.77)	1.32 (0.88-1.97)	0.90 (0.59-1.39)	0.56
Beer					
Case/control (n)	667/654		59/106	101/253	
Multivariable-adjusted OR (95% CI)[d]	1.00		0.53 (0.31-0.93)	0.31 (0.20-0.49)	<.0001
Major animal-based food contributors to NPIP[g]					

Fresh dairy products					
Case/control (n)	107/254	95/253	151/253	474/253	
Multivariable-adjusted OR (95% CI)[d]	1.00	0.83 (0.48-1.44)	1.34 (0.82-2.20)	4.98 (3.20-7.77)	*

a. Quartile cut-off points were determined based on the FFQ-specific control's distribution
b. P-trend was calculated by using the median value of each quartile of NOC consumption as a continuous variable in the multivariable-adjusted model. P-trend was noted as "*", If the linearity assumption was not met after assessing it with the restricted cubic spline function within the logistic model (Pnon-linearity<0.05).
c. It refers to grains not contained in vegetables, fruits, nachos, or mixed dishes. Grains in this study included brown rice, white rice, pasta, oatmeal, bran flakes (breakfast cereal), rye bread, dark bread, popcorn. Grains are the most important contributor to NDEA, NDMA, NMAMBA
d. The model was adjusted for age, total calorie, sex, race, education level, BMI status, alcohol level, history of diabetes and duration combined, smoking status and dose combined, family history of liver cancer (yes, no), HCV status, HBV status
e. Since there was small number of sample size in the first three quartiles, we combined them together as reference group
f. Based on the correlation coefficients in the Supplemental Table 2, the major non-plant food sources of NDMA were pizza, sausage, and beer while the major non-plant sources of NDEA included fresh seafood, fermented cheese and cured lunch meats (r>0.3). Sausage was not included because of too few controls in the higher quartiles
g. Cured lunch meats and fermented cheese products listed in the other section of this table were the other two major animal-based food contributors to NPIP

Supplemental Table 4. Multivariable-adjusted odds ratios and 95% CIs of noncirrhotic HCC risk according to quartiles of consumption of N-Nitroso compounds (mcg per 1000 kcal/day)*

N-nitroso compounds from dietary sources	Quartiles of intake [a]				P-trend[b]
	Q1	Q2	Q3	Q4	
Total N-nitroso compounds[c]					
Case/control	147/254	116/253	86/253	143/253	
Multivariable-adjusted OR (95% CI) [d]	1.00	0.92 (0.57-1.46)	0.62 (0.38-1.03)	1.12 (0.71-1.77)	0.88
Plant sources					
Case/control	143/254	118/253	89/253	142/253	
Multivariable-adjusted OR (95% CI) [e]	1.00	1.02 (0.63-1.63)	0.65 (0.39-1.07)	1.14 (0.72-1.81)	0.89
Animal sources					
Case/control	178/254	86/253	106/253	122/253	
Multivariable-adjusted OR (95% CI)[f]	1.00	0.42 (0.26-0.68)	0.43 (0.26-0.70)	0.67 (0.43-1.06)	*
N-nitrosodiethylamine (NDEA)					
Case/control	110/254	92/253	142/253	148/253	
Multivariable-adjusted OR (95% CI)[d]	1.00	0.56 (0.34-0.94)	1.07 (0.68-1.69)	0.93 (0.58-1.48)	0.87
Plant sources					
Case/control	97/254	102/253	106/253	187/253	
Multivariable-adjusted OR (95% CI)[e]	1.00	0.88 (0.54-1.45)	0.81 (0.49-1.34)	1.42 (0.88-2.28)	0.26
Animal sources					
Case/control	134/254	116/253	115/253	127/253	
Multivariable-adjusted OR (95% CI)[f]	1.00	0.83 (0.51-1.34)	0.53 (0.33-0.87)	0.87 (0.54-1.39)	0.28
N-nitrosodimethylamine (NDMA)					
Case/control	146/254	116/253	110/253	120/253	
Multivariable-adjusted OR (95% CI) [d]	1.00	1.01 (0.64-1.61)	0.79 (0.49-1.29)	0.92 (0.57-1.47)	0.61
Plant sources					
Case/control	101/254	100/253	103/253	188/253	
Multivariable-adjusted OR (95% CI) [e]	1.00	0.89 (0.54-1.47)	0.95 (0.58-1.56)	1.40 (0.87-2.25)	0.20
Animal sources					
Case/control	133/254	128/253	93/253	138/253	
Multivariable-adjusted OR (95% CI)[f]	1.00	1.13 (0.70-1.83)	0.96 (0.58-1.58)	1.31 (0.82-2.08)	0.32
N-nitrosodibutylamine (NDBA)[g]					
Case/control	171/254	112/253	123/253	86/253	
Multivariable-adjusted OR (95% CI) [d,f]	1.00	0.49 (0.31-0.78)	0.70 (0.44-1.12)	**0.37 (0.22-0.60)**	**0.0002**

N-nitrosodipropylamine (NDPA)[g]					
Case/control	161/254	108/253	116/253	107/253	
Multivariable-adjusted OR (95% CI) [d,f]	1.00	0.58 (0.36-0.93)	0.92 (0.57-1.48)	0.79 (0.47-1.31)	0.45
N-nitroso-N-(1-methylacetonyl)-3-methylbutylamine (NMAMBA)					
Case/control	101/254	98/253	126/253	167/253	
Multivariable-adjusted OR(95% CI) [d]	1.00	0.66 (0.40-1.09)	1.13 (0.71-1.81)	1.18 (0.74-1.89)	0.34
Plant sources					
Case/control	97/254	95/253	117/253	183/253	
Multivariable-adjusted OR (95% CI) [e]	1.00	0.83 (0.50-1.37)	0.96 (0.59-1.56)	1.41 (0.87-2.26)	0.19
Animal sources					
Case/control	178/294	112/213	112/253	90/253	
Multivariable-adjusted OR (95% CI) [f]	1.00	1.27 (0.75-2.15)	1.34 (0.84-2.12)	0.97 (0.60-1.57)	0.62
N-nitrosopyrrolidine (NPYR)					
Case/control	143/254	112/253	137/253	100/253	
Multivariable-adjusted OR (95% CI) [d]	1.00	1.14 (0.70-1.84)	1.26 (0.79-2.01)	0.96 (0.60-1.55)	0.94
Plant sources					
Case/control	152/254	89/253	122/253	129/253	
Multivariable-adjusted OR (95% CI) [e]	1.00	0.80 (0.49-1.29)	1.00 (0.63-1.60)	0.71 (0.44-1.15)	0.25
Animal sources					
Case/control	131/254	118/253	110/253	133/253	
Multivariable-adjusted OR (95% CI) [f]	1.00	1.12 (0.70-1.80)	1.08 (0.66-1.77)	1.04 (0.64-1.67)	0.92
N-nitrosopiperidine (NPIP)[g]					
Case/control	90/254	105/253	105/253	192/253	
Multivariable-adjusted OR (95% CI) [d,f]	1.00	1.45 (0.86-2.42)	0.86 (0.50-1.48)	**1.97 (1.21-3.19)**	**0.02**
Nitrate (NO_3)[*]					
Case/control	146/254	114/253	85/253	147/253	
Multivariable-adjusted OR (95% CI)[d]	1.00	0.92 (0.58-1.48)	0.59 (0.36-0.98)	1.18 (0.75-1.85)	0.75
Plant sources					
Case/control	143/254	118/253	89/253	142/253	
Multivariable-adjusted OR (95% CI)[e]	1.00	1.03 (0.64-1.65)	0.65 (0.39-1.08)	1.15 (0.73-1.82)	0.87
Animal sources					
Case/control	191/254	78/253	111/253	112/253	

Multivariable-adjusted OR (95% CI)[f]	1.00	0.37 (0.22-0.62)	0.56 (0.35-0.89)	0.66 (0.42-1.04)	*
Nitrite (NO_2)[g*]					
Case/control	160/254	103/253	104/253	125/253	
Multivariable-adjusted OR (95% CI)[d,f]	1.00	0.50 (0.31-0.81)	0.49 (0.30-0.79)	**0.51 (0.32-0.82)**	**0.001**

* Units for means and ranges of all NOCs consumption in this table are mcg/1000kcal/day, except three compounds: total N-nitroso compounds, Nitrate, Nitrite, which used unit of mg/1000kcal/day.

a. Quartile cut-off points were set as the energy-adjusted log-transformed FFQ-specific value based on control's distribution

b. P-trend was calculated by using the median value of each quartile of NOC consumption as a continuous variable in the multivariable-adjusted model. P-trend was noted as "*", If the linearity assumption was not met after assessing it with the restricted cubic spline function within the logistic model ($P_{non\text{-}linearity}<0.05$).

c. Intake of total N-nitroso compounds capture all the 23 compounds in the N-nitroso database, ie, 21 individual NOCs plus nitrite and nitrate.

d. The model was adjusted for age, total calorie, sex, race, education level, BMI status, alcohol level, history of diabetes and duration combined, smoking status and dose combined, family history of liver cancer, HCV status, HBV status.

e. Multivariable-adjusted model for NOCs from plant sources was additionally adjusted for red and processed meet intake

f. Multivariable-adjusted model for NOCs from animal sources was additionally adjusted for total vegetable and fruit intake

g. Total N-nitroso compounds consumption were all from animal sources.

Supplemental Table 5. Multivariable-adjusted odds ratios and 95% CIs of HCC according to quartiles of consumption of N-Nitroso compounds (mcg per 1000 kcal/day)* among 1,257 subjects who completed the original version of FFQ

N-nitroso compounds from dietary sources	Quartiles of intake[a]				P-trend[b]	P-interaction[c]
	Q1	Q2	Q3	Q4		
Total N-nitroso compounds[d]						
Case/control (n)	108/239	71/239	57/239	65/239		
Multivariable-adjusted OR (95% CI)[e]	1.00	0.91 (0.36-2.25)	0.70 (0.27-1.84)	0.64 (0.26-1.59)	0.30	0.24
Plant sources						
Multivariable-adjusted OR (95% CI)[f]	1.00	0.99 (0.40-2.45)	0.78 (0.30-2.00)	0.63 (0.25-1.56)	0.31	0.18
Animal sources						
Multivariable-adjusted OR (95% CI)[g]	1.00	0.44 (0.17-1.16)	0.57 (0.21-1.55)	0.44 (0.17-1.13)	0.10	0.61
N-nitrosodiethylamine (NDEA)						
Case/control (n)	63/239	84/239	69/239	85/239		
Multivariable-adjusted OR (95% CI)[e]	1.00	1.30 (0.49-3.40)	0.99 (0.38-2.56)	0.72 (0.27-1.91)	0.43	0.21
Plant sources						
Multivariable-adjusted OR (95% CI)[f]	1.00	0.81 (0.30-2.21)	0.44 (0.16-1.18)	0.98 (0.36-2.68)	0.71	0.23
Animal sources						
Multivariable-adjusted OR (95% CI)[g]	1.00	2.46 (0.87-6.90)	0.97 (0.38-2.47)	0.55 (0.21-1.45)	*	0.44
N-nitrosodimethylamine (NDMA)						
Case/control (n)	95/239	62/239	83/239	61/239		
Multivariable-adjusted OR (95% CI)[e]	1.00	0.96 (0.38-2.45)	1.36 (0.53-3.48)	0.60 (0.24-1.51)	0.35	0.61
Plant sources						
Multivariable-adjusted OR (95% CI)[f]	1.00	1.30 (0.47-3.57)	0.53 (0.19-1.42)	1.30 (0.51-3.34)	0.86	0.43
Animal sources						
Multivariable-adjusted OR (95% CI)[g]	1.00	1.14 (0.44-2.98)	0.81 (0.30-2.15)	0.83 (0.33-2.07)	0.61	0.79
N-nitrosodibutylamine (NDBA)[h]						
Case/control (n)	86/239	70/239	74/239	71/239		
Multivariable-adjusted OR (95% CI)[g]	1.00	0.63 (0.25-1.59)	0.51 (0.18-1.39)	0.60 (0.23-1.52)	0.20	0.76
N-nitrosodipropylamine (NDPA)[h]						
Case/control (n)	102/239	78/239	75/239	46/239		

Multivariable-adjusted OR (95% CI)[g]	1.00	0.82 (0.34-1.99)	1.51 (0.60-3.83)	0.57 (0.20-1.61)	0.60	0.16
N-nitroso-N-(1-methylacetonyl)-3-methylbutylamine (NMAMBA)						
Case/control (n)	64/239	71/239	67/239	99/239		
Multivariable-adjusted OR (95% CI)[e]	1.00	0.94 (0.34-2.56)	0.52 (0.20-1.36)	1.21 (0.47-3.12)	0.87	0.02
Plant sources						
Multivariable-adjusted OR (95% CI)[f]	1.00	0.72 (0.26-1.98)	0.38 (0.14-1.02)	1.08 (0.40-2.92)	0.85	0.10
Animal sources						
Multivariable-adjusted OR (95% CI)[g]	1.00	0.65 (0.23-1.82)	0.94 (0.38-2.37)	1.29 (0.53-3.15)	0.77	0.77
N-nitrosopyrrolidine (NPYR)						
Case/control (n)	111/239	64/239	69/239	57/239		
Multivariable-adjusted OR (95% CI)[e]	1.00	0.58 (0.23-1.45)	0.44 (0.17-1.09)	0.61 (0.24-1.56)	0.22	0.23
Plant sources						
Multivariable-adjusted OR (95% CI)[f]	1.00	0.51 (0.19-1.39)	1.13 (0.48-2.69)	0.51 (0.20-1.30)	0.30	0.26
Animal sources						
Multivariable-adjusted OR (95% CI)[g]	1.00	0.29 (0.10-0.83)	0.45 (0.16-1.29)	0.31 (0.12-0.82)	0.06	0.58
N-nitrosopiperidine (NPIP)[h]						
Case/control (n)	59/239	68/239	73/239	101/239		
Multivariable-adjusted OR (95% CI)[g]	1.00	1.71 (0.59-4.93)	1.16 (0.41-3.28)	0.85 (0.31-2.32)	0.58	0.65
Nitrate (NO_3)*						
Case/control (n)	108/239	72/239	57/239	64/239		
Multivariable-adjusted OR (95% CI)[e]	1.00	1.08 (0.43-2.68)	0.69 (2.67-1.79)	0.68 (0.27-1.67)	0.31	0.20
Plant sources						
Multivariable-adjusted OR (95% CI)[f]	1.00	0.99 (0.40-2.45)	0.78 (0.30-2.00)	0.63 (0.25-1.56)	0.31	0.18
Animal sources						
Multivariable-adjusted OR (95% CI)[g]	1.00	0.30 (0.11-0.79)	0.61 (0.23-1.62)	0.41 (0.16-1.02)	0.07	0.43
Nitrite (NO_2)[h]*						
Case/control (n)	74/239	70/239	70/239	87/239		
Multivariable-adjusted OR (95% CI)[g]	1.00	0.68 (0.25-1.86)	0.68 (0.24-1.86)	0.58 (0.23-1.44)	0.24	0.90

* The units for all N-nitroso compounds consumption in this table are mcg/1000kcal/day, except three compounds: total N-nitroso compounds, Nitrate, Nitrite, which used unit of mg/1000kcal/day.

a. Quartile cut-off points were determined based on the FFQ-specific control's distribution
b. P-trend was calculated by using the median value of each quartile of N-nitroso compound consumption as a continuous variable in the multivariable-adjusted model, "*" notes the significant non-linearity
c. P-interaction was assessed by adding the cross-product of version of FFQ and individual NOC in the multivariable-adjusted model among all the subjects
d. Intake of total N-nitroso compounds capture all the 23 compounds in the N-nitroso database. Unit of intake of total N-nitroso compounds is mg/1000kcal/day.
e. The multivariable-adjusted model was adjusted for age, total calorie, sex, race, education level, BMI status, alcohol level, history of diabetes and duration combined, smoking status and dose combined, family history of liver cancer, HCV status (negative, positive, missing), HBV status (negative, positive, missing).
f. Multivariable-adjusted model for N-nitroso compounds from plant sources additionally adjusted for red and processed meet intake level (classified as four-level categorical)
g. Multivariable-adjusted model for N-nitroso compounds from animal sources additionally adjusted for total vegetable and fruit intake level (classified as four-level categorical)
h. Total N-nitroso compounds consumption were all from animal sources.