Supplemental Table 1. Risk of colon cancer according to baseline quintiles of one-carbon nutrient intake by micro satellite instability (MSI) status of tumor among 47,371 men and 88,691 women (NHS and HPFS separately and combined).

Energy-adjusted daily one-carbon nutrient intake	RR (95% CI)*					P_{trend}
Folate (µg)	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	
	Nurses' Health Study					
Folate, range (µg)	**≤190**	**191-245**	**246-318**	**319-549**	**≥550**	
Cases / Person-years	89/373965	91/373326	68/372686	68/373129	73/368818	
All cancers‡	1.0	0.94 (0.70-1.26)	0.66 (0.48-0.90)	0.65 (0.48-0.90)	0.71 (0.52-0.97)	0.09
All cancers*	1.0	0.97 (0.72-1.30)	0.70 (0.51-0.96)	0.71 (0.51-0.98)	0.80 (0.58-1.10)	0.34
Cases / Person-years	72/373978	74/373343	52/372697	56/373142	56/368838	
MSI-low/MSS‡	1.0	1.06 (0.77-1.47)	0.62 (0.44-0.89)	0.67 (0.47-0.95)	0.68 (0.48-0.96)	0.05
MSI-low/MSS*	1.0	1.03 (0.74-1.43)	0.66 (0.46-0.95)	0.72 (0.51-1.03)	0.76 (0.53-1.09)	0.18
Cases / Person-years	17/374027	17/37385	16/372727	12/373176	17/368862	
MSI-high‡	1.0	0.92 (0.47-1.79)	0.81 (0.41-1.60)	0.60 (0.29-1.26)	0.87 (0.44-1.70)	0.86
MSI-high*	1.0	0.94 (0.48-1.85)	0.86 (0.43-1.70)	0.65 (0.31-1.37)	0.97 (0.49-1.92)	0.62
	Health Professionals Follow-up Study					
Folate, range (µg)	**≤284**	**285-351**	**352-437**	**438-661**	**≥662**	
Cases / Person-years	59/148506	56/147823	53/147593	55/147610	54/145950	
All cancers‡	1.0	0.87 (0.60-1.25)	0.79 (0.54-1.14)	0.81 (0.56-1.17)	0.76 (0.52-1.10)	0.06
All cancers*	1.0	0.87 (0.60-1.25)	0.81 (0.56-1.18)	0.86 (0.59-1.25)	0.80 (0.54-1.19)	0.14
Cases / Person-years	45/148506	48/147823	46/147593	49/147610	50/145950	
MSI-low/MSS‡	1.0	1.03 (0.68-1.54)	0.89 (0.59-1.35)	0.95 (0.63-1.42)	0.92 (0.61-1.38)	0.18
MSI-low/MSS*	1.0	1.03 (0.68-1.55)	0.93 (0.61-1.40)	1.00 (0.66-1.52)	0.98 (0.64-1.50)	0.26
Cases / Person-years	14/148506	8/147823	7/147593	6/147610	4/145950	
MSI-high‡	1.0	0.52 (0.22-1.24)	0.44 (0.18-1.08)	0.37 (0.14-0.97)	0.24 (0.08-0.72)	0.13
MSI-high*	1.0	0.52 (0.22-1.24)	0.45 (0.18-1.11)	0.39 (0.15-1.02)	0.25 (0.08-0.76)	0.22
	Both Cohorts Combined					
Cases / Person-years	148/515784	147/514680	121/513801	123/514473	127/508147	

All cancers‡	1.0	0.91 (0.72-1.14)	0.71 (0.56-0.90)	0.71 (0.56-0.91)	0.73 (0.58-0.93)	0.03
All cancers*	1.0	0.92 (0.73-1.16)	0.74 (0.58-0.94)	0.77 (0.60-0.98)	0.80 (0.62-1.03)	0.09
Cases / Person-years	117/515809	122/514707	98/513818	105/514492	106/508170	
MSI-low/MSS‡	1.0	1.05 (0.81-1.35)	0.72 (0.55-0.95)	0.77 (0.59-1.01)	0.77 (0.59-1.00)	0.06
MSI-low/MSS*	1.0	1.03 (0.80-1.33)	0.76 (0.58-0.99)	0.83 (0.63-1.08)	0.84 (0.64-1.11)	0.13
Cases / Person-years	31/515889	25/514780	23/513884	18/514570	21/508234	
MSI-high‡	1.0	0.71 (0.44-1.25)	0.64 (0.37-1.10)	0.50 (0.28-0.89)	0.58 (0.33-1.00)	0.36
MSI-high*	1.0	0.75 (0.44-1.27)	0.69 (0.39-1.15)	0.53 (0.30-0.96)	0.63 (0.36-1.10)	0.45

Methionine (g)	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	
			Nurses' Health Study			
Methionine, range (g)	**≤1.50**	**1.51-1.70**	**1.71-1.90**	**1.91-2.20**	**≥2.21**	
Cases / Person-years	82/371361	91/371700	65/375393	63/372420	88/371050	
All cancers‡	1.0	1.10 (0.81-1.48)	0.76 (0.55-1.05)	0.72 (0.52-1.00)	0.95 (0.70-1.28)	0.71
All cancers*	1.0	1.08 (0.80-1.46)	0.73 (0.52-1.02)	0.70 (0.50-0.98)	0.92 (0.68-1.26)	0.68
Cases / Person-years	64/371378	74/371717	56/375400	45/372437	71/371066	
MSI-low/MSS‡	1.0	0.88 (0.63-1.23)	0.83 (0.58-1.19)	0.66 (0.45-0.97)	0.98 (0.70-1.37)	0.60
MSI-low/MSS*	1.0	0.89 (0.64-1.25)	0.81 (0.56-1.16)	0.64 (0.43-0.94)	0.96 (0.68-1.35)	0.32
Cases / Person-years	18/371415	17/371764	9/375440	18/372455	17/371103	
MSI-high‡	1.0	0.93 (0.48-1.81)	0.48 (0.21-1.06)	0.94 (0.49-1.80)	0.83 (0.43-1.61)	0.81
MSI-high*	1.0	0.92 (0.47-1.78)	0.46 (0.21-1.03)	0.91 (0.47-1.75)	0.82 (0.42-1.59)	0.05
			Health Professionals Follow-up Study			
Methionine, range (g)	**≤1.81**	**1.82-2.04**	**2.05-2.26**	**2.27-2.54**	**≥2.55**	
Cases / Person-years	66/146799	56/147801	43/149252	70/147413	42/146217	
All cancers‡	1.0	0.86 (0.60-1.22)	0.65 (0.44-0.96)	1.05 (0.75-1.47)	0.59 (0.40-0.87)	0.03
All cancers*	1.0	0.83 (0.58-1.18)	0.62 (0.42-0.92)	1.02 (0.72-1.43)	0.60 (0.40-0.89)	0.04
Cases / Person-years	56/146799	52/147801	31/149252	65/147413	34/146217	
MSI-low/MSS‡	1.0	1.07 (0.73-1.56)	0.55 (0.36-0.86)	1.14 (0.80-1.64)	0.56 (0.37-0.86)	0.03
MSI-low/MSS*	1.0	1.11 (0.76-1.62)	0.53 (0.34-0.82)	1.11 (0.77-1.60)	0.57 (0.37-0.88)	0.04
Cases / Person-years	10/146799	4/147801	12/149252	5/147413	8/146217	
MSI-high‡	1.0	0.41 (0.13-1.29)	1.20 (0.52-2.78)	0.50 (0.17-1.45)	0.75 (0.30-1.90)	0.60

MSI-high*	1.0	0.39 (0.12-1.29)	1.15 (0.50-2.66)	0.48 (0.16-1.41)	0.76 (0.30-1.93)	0.62
			Both Cohorts Combined			
Cases / Person-years	148/511849	147/513305	108/518361	133/513171	130/510198	
All cancers‡	1.0	0.99 (0.79-1.24)	0.71 (0.55-0.91)	0.86 (0.68-1.09)	0.79 (0.62-1.00)	0.30
All cancers*	1.0	0.97 (0.77-1.22)	0.69 (0.54-0.89)	0.84 (0.66-1.07)	0.79 (0.62-1.00)	0.11
Cases / Person-years	120/511878	126/513325	87/518378	110/513192	105/510222	
MSI-low/MSS‡	1.0	0.96 (0.74-1.23)	0.71 (0.54-0.93)	0.88 (0.68-1.14)	0.79 (0.60-1.02)	0.36
MSI-low/MSS*	1.0	0.98 (0.75-1.26)	0.69 (0.52-0.91)	0.86 (0.66-1.12)	0.78 (0.60-1.02)	0.15
Cases / Person-years	28/511955	21/513419	21/518431	23/513266	25/510285	
MSI-high‡	1.0	0.75 (0.42-1.32)	0.73 (0.41-1.28)	0.79 (0.45-1.37)	0.80 (0.47-1.38)	0.62
MSI-high*	1.0	0.73 (0.42-1.29)	0.71 (0.40-1.25)	0.77 (0.44-1.34)	0.80 (0.47-1.38)	0.44

Vitamin B_6 (mg)	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**P Trend**
			Nurses' Health Study			
Vitamin B_6, range (mg)	**≤1.30**	**1.31-1.60**	**1.61-2.00**	**2.01-3.50**	**≥3.51**	
Cases / Person-years	93/375527	77/372932	72/374307	66/371265	81/367893	
All cancers‡	1.0	0.77 (0.57-1.04)	0.65 (0.48-0.89)	0.62 (0.45-0.85)	0.74 (0.55-1.00)	0.50
All cancers*	1.0	0.77 (0.57-1.04)	0.67 (0.49-0.92)	0.66 (0.48-0.91)	0.82 (0.60-1.13)	0.33
Cases / Person-years	73/375547	65/372939	58/374321	55/371275	59/367917	
MSI-low/MSS‡	1.0	1.21 (0.87-1.69)	0.67 (0.47-0.95)	0.66 (0.46-0.93)	0.69 (0.49-0.97)	0.77
MSI-low/MSS*	1.0	1.21 (0.86-1.69)	0.69 (0.49-0.98)	0.70 (0.49-1.00)	0.76 (0.53-1.09)	0.58
Cases / Person-years	20/375590	12/372979	14/374359	11/371309	22/367940	
MSI-high‡	1.0	0.56 (0.27-1.14)	0.61 (0.31-1.20)	0.51 (0.24-1.07)	1.04 (0.56-1.92)	0.41
MSI-high*	1.0	0.56 (0.27-1.14)	0.59 (0.30-1.17)	0.48 (0.23-1.00)	0.93 (0.51-1.71)	0.34
			Health Professionals Follow-up Study			
Vitamin B_6, range (mg)	**≤1.90**	**1.91-2.30**	**2.31-3.10**	**3.11-5.80**	**≥5.81**	
Cases / Person-years	57/149632	64/148798	55/146834	43/146568	58/145650	
All cancers‡	1.0	1.00 (0.70-1.43)	0.76 (052-1.10)	0.59 (0.40-0.88)	0.80 (0.55-1.15)	0.96
All cancers*	1.0	1.01 (0.70-1.44)	0.79 (0.54-1.15)	0.59 (0.39-0.89)	0.82 (0.55-1.22)	0.67
Cases / Person-years	48/149632	56/148798	42/146834	39/146568	53/145650	
MSI-low/MSS‡	1.0	0.96 (0.65-1.41)	0.69 (0.45-1.04)	0.63 (0.42-0.97)	0.87 (0.59-1.28)	0.83

MSI-low/MSS*	1.0	0.96 (0.65-1.41)	0.72 (0.47-1.09)	0.64 (0.41-0.99)	0.89 (0.58-1.36)	0.56
Cases / Person-years	9/149632	8/148798	13/146834	4/146568	5/145650	
MSI-high‡	1.0	0.79 (0.31-2.06)	1.14 (0.49-2.67)	0.35 (0.11-1.13)	0.44 (0.15-1.31)	0.67
MSI-high*	1.0	0.80 (0.31-2.07)	1.18 (0.50-2.77)	0.35 (0.11-1.14)	0.45 (0.15-1.36)	0.78
			Both Cohorts Combined			
Cases / Person-years	150/518899	141/515313	127/514523	109/511352	139/506798	
All cancers‡	1.0	0.86 (0.68-1.08)	0.69 (0.55-0.88)	0.61 (0.47-0.78)	0.76 (0.60-0.96)	0.54
All cancers*	1.0	0.87 (0.69-1.09)	0.72 (0.57-0.91)	0.64 (0.49-0.82)	0.83 (0.65-1.06)	0.38
Cases / Person-years	121/518928	121/515327	100/514550	94/511365	112/506827	
MSI-low/MSS‡	1.0	1.09 (0.85-1.41)	0.68 (0.52-0.88)	0.65 (0.49-0.85)	0.76 (0.59-0.99)	0.45
MSI-low/MSS*	1.0	1.09 (0.84-1.40)	0.70 (0.54-0.92)	0.68 (0.52-0.90)	0.83 (0.63-1.08)	0.32
Cases / Person-years	29/519006	20/515409	27/514612	15/511431	27/506898	
MSI-high‡	1.0	0.63 (0.36-1.11)	0.76 (0.45-1.28)	0.43 (0.23-0.80)	0.77 (0.45-1.29)	0.88
MSI-high*	1.0	0.64 (0.36-1.12)	0.79 (0.47-1.34)	0.45 (0.24-0.85)	0.84 (0.49-1.42)	0.96

Vitamin B_{12} (g)	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	**P Trend**
			Nurses' Health Study			
Vitamin B_{12}, range (g)	**≤4.0**	**4.1-5.0**	**5.1-7.0**	**7.1-11.0**	**≥11.1**	
Cases / Person-years	75/374299	89/373459	62/373486	80/371351	83/369329	
All cancers‡	1.0	1.13 (0.83-1.54)	0.76 (0.54-1.06)	0.96 (0.70-1.32)	0.93 (0.68-1.27)	0.76
All cancers*	1.0	1.13 (0.83-1.54)	0.76 (0.54-1.06)	0.99 (0.72-1.36)	0.95 (0.69-1.31)	0.97
Cases / Person-years	59/374314	69/373475	55/373493	60/371371	67/369345	
MSI-low/MSS‡	1.0	0.90 (0.63-1.27)	0.86 (0.59-1.23)	0.92 (0.64-1.32)	0.96 (0.67-1.36)	0.66
MSI-low/MSS*	1.0	0.90 (0.64-1.28)	0.85 (0.59-1.23)	0.94 (0.65-1.35)	0.98 (0.69-1.40)	0.84
Cases / Person-years	16/374349	20/373514	7/373534	20/371396	16/369385	
MSI-high‡	1.0	1.19 (0.62-2.30)	0.40 (0.17-0.97)	1.13 (0.58-2.18)	0.84 (0.42-1.68)	0.86
MSI-high*	1.0	1.19 (0.62-2.29)	0.40 (0.16-0.97)	1.15 (0.60-2.23)	0.86 (0.43-1.73)	0.75
			Health Professionals Follow-up Study			
Vitamin B_{12}, range (g)	**≤6.0**	**6.1-8.0**	**8.1-11.0**	**11.1-16.0**	**≥16.1**	
Cases / Person-years	66/148858	42/148915	66/147747	50/146008	53/145954	
All cancers‡	1.0	0.64 (0.43-0.94)	0.96 (0.68-1.35)	0.67 (0.46-0.97)	0.73 (0.51-1.04)	0.14

All cancers*	1.0	0.58 (0.39-0.86)	0.88 (0.62-1.24)	0.61 (0.41-0.89)	0.66 (0.45-0.97)	0.73
Cases / Person-years	56/148858	38/148915	56/147747	43/146008	45/145954	
MSI-low/MSS‡	1.0	1.48 (0.98-2.23)	0.96 (0.66-1.39)	0.68 (0.46-1.01)	0.73 (0.49-1.07)	0.89
MSI-low/MSS*	1.0	1.62 (1.07-2.46)	0.88 (0.60-1.28)	0.61 (0.41-0.93)	0.66 (0.44-1.00)	0.92
Cases / Person-years	10/148858	4/148915	10/147747	7/146008	8/145954	
MSI-high‡	1.0	0.40 (0.13-1.27)	0.96 (0.40-2.31)	0.62 (0.24-1.62)	0.72 (0.29-1.84)	0.33
MSI-high*	1.0	0.36 (0.11-1.16)	0.88 (0.36-2.12)	0.56 (0.21-1.48)	0.66 (0.26-1.69)	0.32
			Both Cohorts Combined			
Cases / Person-years	141/516644	131/516089	128/514978	130/510810	136/508365	
All cancers‡	1.0	0.90 (0.71-1.14)	0.85 (0.67-1.08)	0.82 (0.65-1.05)	0.83 (0.66-1.05)	0.75
All cancers*	1.0	0.88 (0.69-1.11)	0.83 (0.65-1.05)	0.82 (0.65-1.05)	0.83 (0.65-1.06)	0.81
Cases / Person-years	115/516669	107/516109	111/514996	103/510836	112/508387	
MSI-low/MSS‡	1.0	1.11 (0.85-1.44)	0.90 (0.69-1.17)	0.80 (0.61-1.04)	0.84 (0.65-1.09)	0.85
MSI-low/MSS*	1.0	1.14 (0.88-1.49)	0.88 (0.68-1.14)	0.80 (0.61-1.05)	0.84 (0.64-1.09)	0.90
Cases / Person-years	26/516746	24/516186	17/515070	27/510895	24/508459	
MSI-high‡	1.0	0.90 (0.51-1.56)	0.61 (0.33-1.12)	0.93 (0.54-1.59)	0.80 (0.46-1.39)	0.72
MSI-high*	1.0	0.87 (0.50-1.51)	0.59 (0.32-1.10)	0.93 (0.54-1.59)	0.80 (0.46-1.39)	0.73

Alcohol (g)	**No alcohol**	**<5 g/day**	**5-14.9 g/day**	**≥15 g/day**	**P Trend**
		Nurses' Health Study			
Cases / Person-years	113/595227	145/629277	82/416136	49/221284	
All cancers‡	1.0	1.28 (1.00-1.64)	1.04 (0.78-1.38)	1.12 (0.80-1.57)	0.99
All cancers*	1.0	1.32 (1.03-1.70)	1.09 (0.81-1.46)	1.14 (0.80-1.61)	0.91
Cases / Person-years	85/595253	122/629298	65/416152	38/221295	
MSI-low/MSS‡	1.0	0.70 (0.53-0.92)	1.10 (0.79-1.51)	1.16 (0.79-1.70)	0.58
MSI-low/MSS*	1.0	0.68 (0.51-0.89)	1.15 (0.82-1.59)	1.17 (0.79-1.73)	0.52
Cases / Person-years	28/595293	23/629378	17/416190	11/221316	
MSI-high‡	1.0	0.82 (0.47-1.42)	0.87 (0.48-1.58)	1.01 (0.51-2.04)	0.26
MSI-high*	1.0	0.85 (0.49-1.47)	0.91 (0.49-1.66)	1.03 (0.51-2.08)	0.30
		Health Professionals Follow-up Study			
Cases / Person-years	60/172697	43/179417	78/201738	96/183630	

All cancers‡	1.0	0.73 (0.49-1.08)	1.16 (0.83-1.62)	1.49 (1.08-2.06)	0.001
All cancers*	1.0	0.72 (0.49-1.07)	1.13 (0.80-1.59)	1.44 (1.03-2.01)	0.01
Cases / Person-years	51/172697	34/179417	67/201738	86/183630	
MSI-low/MSS‡	1.0	1.48 (0.96-2.28)	1.17 (0.81-1.69)	1.57 (1.11-2.22)	0.0004
MSI-low/MSS*	1.0	1.48 (0.96-2.29)	1.14 (0.79-1.65)	1.52 (1.06-2.17)	0.002
Cases / Person-years	9/172697	9/179417	11/201738	10/183630	
MSI-high‡	1.0	1.01 (0.40-2.55)	1.08 (0.45-2.60)	1.03 (0.42-2.53)	0.89
MSI-high*	1.0	1.00 (0.40-2.53)	1.04 (0.43-2.53)	0.99 (0.40-2.43)	0.78
	Both Cohorts Combined				
Cases / Person-years	173/759596	188/801010	160/609377	145/396902	
All cancers‡	1.0	1.09 (0.89-1.34)	1.11 (0.90-1.38)	1.40 (1.12-1.74)	0.004
All cancers*	1.0	1.11 (0.90-1.37)	1.12 (0.90-1.40)	1.34 (1.06-1.69)	0.05
Cases / Person-years	136/759631	156/801042	132/609402	124/396921	
MSI-low/MSS‡	1.0	0.87 (0.69-1.09)	1.17 (0.92-1.49)	1.52 (1.19-1.94)	0.003
MSI-low/MSS*	1.0	0.85 (0.68-1.08)	1.18 (0.92-1.51)	1.46 (1.13-1.88)	0.03
Cases / Person-years	37/759710	32/801143	28/609493	21/397009	
MSI-high‡	1.0	0.87 (0.54-1.39)	0.90 (0.55-1.48)	0.93 (0.55-1.59)	0.69
MSI-high*	1.0	0.88 (0.55-1.41)	0.91 (0.55-1.49)	0.89 (0.52-1.53)	0.94

‡ Age-adjusted only.

*All models are adjusted for age (continuous), energy intake, gender, screening sigmoidoscopy, family history of colorectal cancer, aspirin use, smoking, physical activity in METs, baseline body mass index, a history of colon polyps, beef intake, calcium, multi-vitamin use, and baseline folate, vitamin B6, B12, methionine, and alcohol if not primary exposure.

Abbreviations: MSI, microsatellite instability; MSS, microsatellite stable.

Supplemental Table 2. Risk of colon cancer according to baseline quintiles of one-carbon nutrient intake by *KRAS* mutation status of tumor among 47,371 men and 88,691 women (NHS and HPFS separately and combined).

Energy-adjusted daily one-carbon nutrient intake	RR (95% CI)*					P trend
Folate (µg)	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	
	Nurses' Health Study					
Folate, range (µg)	**≤190**	**191-245**	**246-318**	**319-549**	**≥550**	
Cases / Person-years	89/373965	91/373326	70/372683	68/373129	73/368818	
All cancers‡	1.0	0.94 (0.70-1.26)	0.68 (0.50-0.93)	0.65 (0.48-0.90)	0.71 (0.52-0.97)	0.09
All cancers*	1.0	0.97 (0.72-1.30)	0.72 (0.52-0.99)	0.71 (0.51-0.98)	0.80 (0.58-1.11)	0.33
Cases / Person-years	66/373987	64/373351	47/372706	44/373146	51/368837	
KRAS-wildtype‡	1.0	1.12 (0.80-1.58)	0.62 (0.42-0.89)	0.57 (0.39-0.84)	0.67 (0.47-0.97)	0.15
KRAS-wildtype*	1.0	1.09 (0.77-1.54)	0.65 (0.45-0.95)	0.62 (0.42-0.91)	0.75 (0.52-1.10)	0.39
Cases / Person-years	23/374019	27/373377	23/372716	24/373171	22/368863	
KRAS-mutated‡	1.0	1.08 (0.62-1.88)	0.86 (0.48-1.54)	0.89 (0.50-1.58)	0.83 (0.46-1.49)	0.37
KRAS-mutated*	1.0	1.11 (0.64-1.94)	0.91 (0.51-1.63)	0.97 (0.55-1.72)	0.93 (0.51-1.68)	0.61
	Health Professionals Follow-up Study					
Folate, range (µg)	**≤284**	**285-351**	**352-437**	**438-661**	**≥662**	
Cases / Person-years	58/148506	57/147861	52/147593	57/147624	54/145970	
All cancers‡	1.0	0.90 (0.62-1.29)	0.78 (0.54-1.14)	0.85 (0.59-1.23)	0.77 (0.53-1.12)	0.06
All cancers*	1.0	0.89 (0.62-1.29)	0.81 (0.55-1.18)	0.90 (0.62-1.31)	0.82 (0.55-1.21)	0.15
Cases / Person-years	30/148506	31/147861	31/147593	37/147624	26/145970	
KRAS-wildtype‡	1.0	1.06 (0.64-1.75)	0.90 (0.55-1.49)	1.07 (0.66-1.73)	0.72 (0.42-1.21)	0.17
KRAS-wildtype*	1.0	1.06 (0.64-1.76)	0.93 (0.56-1.54)	1.13 (0.69-1.84)	0.76 (0.44-1.31)	0.29
Cases / Person-years	28/148506	26/147861	21/147593	20/147624	28/145970	
KRAS-mutated‡	1.0	0.85 (0.50-1.45)	0.66 (0.37-1.16)	0.62 (0.35-1.10)	0.83 (0.49-1.40)	0.19
KRAS-mutated*	1.0	0.84 (0.49-1.44)	0.68 (0.38-1.19)	0.65 (0.37-1.17)	0.87 (0.51-1.50)	0.29
	Both Cohorts Combined					
Cases / Person-years	147/515785	158/514712	122/513800	125/514484	127/508166	

All cancers[‡]	1.0	0.92 (0.73-1.16)	0.72 (0.57-0.91)	0.73 (0.58-0.93)	0.74 (0.58-0.93)	0.04
All cancers[*]	1.0	0.94 (0.74-1.18)	0.75 (0.59-0.96)	0.78 (0.61-1.00)	0.80 (0.62-1.03)	0.09
Cases / Person-years	96/515833	95/514761	781/513840	81/514523	77/508207	
KRAS-wildtype[‡]	1.0	1.10 (0.83-1.47)	0.70 (0.52-0.95)	0.73 (0.54-0.98)	0.68 (0.51-0.92)	0.04
KRAS-wildtype[*]	1.0	1.09 (0.82-1.45)	0.73 (0.54-0.99)	0.78 (0.58-1.05)	0.75 (0.55-1.02)	0.08
Cases / Person-years	51/515866	53/514791	44/513861	44/514562	50/508235	
KRAS-mutated[‡]	1.0	0.95 (0.65-1.40)	0.75 (0.50-1.12)	0.74 (0.50-1.11)	0.83 (0.56-1.23)	0.46
KRAS-mutated[*]	1.0	0.97 (0.66-1.42)	0.78 (0.52-1.17)	0.79 (0.53-1.19)	0.91 (0.61-1.35)	0.60

Methionine (g)	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	
			Nurses' Health Study			
Methionine, range (g)	**≤1.50**	**1.51-1.70**	**1.71-1.90**	**1.91-2.20**	**≥2.21**	
Cases / Person-years	82/371361	91/371700	65/375393	63/372420	90/371047	
All cancers[‡]	1.0	1.10 (0.81-1.48)	0.76 (0.55-1.05)	0.72 (0.52-1.00)	0.97 (0.72-1.31)	0.80
All cancers[*]	1.0	1.08 (0.80-1.45)	0.73 (0.52-1.02)	0.70 (0.50-0.98)	0.95 (0.70-1.29)	0.78
Cases / Person-years	58/371380	66/371722	39/375420	45/372437	64/371068	
KRAS-wildtype[‡]	1.0	0.89 (0.63-1.27)	0.64 (0.43-0.96)	0.73 (0.49-1.08)	0.97 (0.68-1.39)	0.84
KRAS-wildtype[*]	1.0	0.91 (0.64-1.29)	0.62 (0.41-0.93)	0.71 (0.47-1.05)	0.95 (0.66-1.37)	0.81
Cases / Person-years	24/371413	25/371759	26/375420	18/372455	26/371099	
KRAS-mutated[‡]	1.0	1.03 (0.59-1.80)	1.03 (0.59-1.80)	0.70 (0.38-1.30)	0.96 (0.55-1.67)	0.88
KRAS-mutated[*]	1.0	1.01 (0.58-1.77)	1.00 (0.57-1.74)	0.68 (0.37-1.26)	0.94 (0.54-1.64)	0.87
			Health Professionals Follow-up Study			
Methionine, range (g)	**≤1.81**	**1.82-2.04**	**2.05-2.26**	**2.27-2.54**	**≥2.55**	
Cases / Person-years	67/146855	56/147814	44/149252	69/147417	42/146217	
All cancers[‡]	1.0	0.85 (0.59-1.20)	0.66 (0.45-0.96)	1.02 (0.73-1.42)	0.58 (0.39-0.85)	0.02
All cancers[*]	1.0	0.82 (0.57-1.17)	0.64 (0.43-0.93)	1.01 (0.71-1.42)	0.61 (0.41-0.90)	0.05
Cases / Person-years	37/146855	33/147814	20/149252	36/147417	29/146217	
KRAS-wildtype[‡]	1.0	1.11 (0.70-1.78)	0.54 (0.31-0.93)	0.96 (0.61-1.52)	0.72 (0.45-1.18)	0.33
KRAS-wildtype[*]	1.0	1.15 (0.72-1.84)	0.52 (0.30-0.90)	0.95 (0.60-1.52)	0.76 (0.46-1.24)	0.44
Cases / Person-years	30/146855	23/147814	24/149252	33/147417	13/146217	
KRAS-mutated[‡]	1.0	0.78 (0.45-1.34)	0.80 (0.47-1.37)	1.09 (0.66-1.78)	0.40 (0.21-0.77)	0.02

KRAS-mutated[*]	1.0	0.75 (0.44-1.30)	0.78 (0.45-1.33)	1.08 (0.65-1.78)	0.42 (0.22-0.81)	0.03
			Both Cohorts Combined			
Cases / Person-years	149/511899	147/513315	109.518360	132/513177	132/510196	
All cancers[‡]	1.0	0.98 (0.78-1.24)	0.71 (0.56-0.91)	0.85 (0.67-1.07)	0.80 (0.63-1.01)	0.31
All cancers[*]	1.0	0.96 (0.77-1.21)	0.69 (0.54-0.89)	0.84 (0.66-1.06)	0.80 (0.63-1.02)	0.14
Cases / Person-years	95/511945	99/513361	59/518905	81/513222	93/510231	
KRAS-wildtype[‡]	1.0	0.96 (0.73-1.28)	0.61 (0.44-0.84)	0.82 (0.61-1.10)	0.88 (0.66-1.17)	0.36
KRAS-wildtype[*]	1.0	0.98 (0.74-1.30)	0.59 (0.42-0.82)	0.80 (0.60-1.09)	0.88 (0.66-1.18)	0.19
Cases / Person-years	54/511988	48/513404	50/518403	51/513246	39/510274	
KRAS-mutated[‡]	1.0	0.89 (0.60-1.31)	0.90 (0.61-1.32)	0.91 (0.62-1.33)	0.65 (0.43-0.98)	0.63
KRAS-mutated[*]	1.0	0.87 (0.59-1.28)	0.88 (0.60-1.29)	0.89 (0.61-1.31)	0.65 (0.43-0.99)	0.42

Vitamin B_6 (mg)	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	
			Nurses' Health Study			
Vitamin B_6, range (mg)	**≤1.30**	**1.31-1.60**	**1.61-2.00**	**2.01-3.50**	**≥3.51**	
Cases / Person-years	93/375527	77/372932	72/374307	68/371263	81/367893	
All cancers[‡]	1.0	0.77 (0.57-1.04)	0.65 (0.48-0.89)	0.64 (0.47-0.87)	0.74 (0.55-1.00)	0.51
All cancers[*]	1.0	0.77 (0.57-1.04)	0.67 (0.49-0.92)	0.68 (0.49-0.94)	0.83 (0.60-1.13)	0.34
Cases / Person-years	68/375551	54/372951	46/374333	43/371280	61/367912	
KRAS-wildtype[‡]	1.0	1.36 (0.95-1.94)	0.57 (0.39-0.83)	0.55 (0.38-0.81)	0.76 (0.54-1.08)	0.25
KRAS-wildtype[*]	1.0	1.35 (0.95-1.94)	0.59 (0.40-0.86)	0.59 (0.40-0.87)	0.85 (0.59-1.22)	0.16
Cases / Person-years	25/375586	23/372967	26/374347	25/371301	20/367945	
KRAS-mutated[‡]	1.0	0.85 (0.48-1.50)	0.88 (0.51-1.52)	0.87 (0.50-1.52)	0.68 (0.38-1.23)	0.38
KRAS-mutated[*]	1.0	0.86 (0.49-1.51)	0.90 (0.52-1.57)	0.93 (0.53-1.63)	0.76 (0.42-1.37)	0.49
			Health Professionals Follow-up Study			
Vitamin B_6, range (mg)	**≤1.90**	**1.91-2.30**	**2.31-3.10**	**3.11-5.80**	**≥5.81**	
Cases / Person-years	56/149632	65/148850	55/147834	43/146568	59/145671	
All cancers[‡]	1.0	1.03 (0.72-1.48)	0.77 (0.53-1.12)	0.60 (0.40-0.89)	0.83 (0.57-1.19)	0.97
All cancers[*]	1.0	1.04 (0.72-1.49)	0.80 (0.55-1.16)	0.60 (0.39-0.91)	0.84 (0.57-1.26)	0.68
Cases / Person-years	26/149632	35/148850	38/147834	21/146568	35/145671	
KRAS-wildtype[‡]	1.0	0.84 (0.50-1.39)	1.15 (0.70-1.89)	0.63 (0.35-1.12)	1.05 (0.63-1.75)	0.28

KRAS-wildtype*	1.0	0.83 (0.50-1.38)	1.19 (0.72-1.96)	0.63 (0.35-1.14)	1.08 (0.63-1.83)	0.16
Cases / Person-years	30/149632	30/148850	17/147834	22/146568	24/145671	
KRAS-mutated‡	1.0	0.89 (0.54-1.48)	0.45 (0.25-0.81)	0.57 (0.33-0.99)	0.63 (0.37-1.08)	0.25
KRAS-mutated*	1.0	0.90 (0.54-1.49)	0.46 (0.25-0.84)	0.57 (0.32-1.00)	0.64 (0.37-1.12)	0.33
			Both Cohorts Combined			
Cases / Person-years	149/518900	142/515357	127/514523	111/511350	140/506817	
All cancers‡	1.0	0.87 (0.69-1.10)	0.70 (0.55-0.88)	0.62 (0.48-0.79)	0.77 (0.61-0.97)	0.54
All cancers*	1.0	0.88 (0.70-1.10)	0.72 (0.57-0.92)	0.65 (0.51-0.84)	0.84 (0.66-1.07)	0.40
Cases / Person-years	94/518953	89/515401	84/514565	84/511386	96/506858	
KRAS-wildtype‡	1.0	1.16 (0.87-1.55)	0.73 (0.54-0.98)	0.57 (0.41-0.78)	0.84 (0.63-1.12)	0.15
KRAS-wildtype*	1.0	1.15 (0.86-1.54)	0.76 (0.56-1.02)	0.60 (0.43-0.82)	0.91 (0.68-1.23)	0.09
Cases / Person-years	55/518981	53/515423	43/514597	47/511408	44/506906	
KRAS-mutated‡	1.0	0.88 (0.60-1.28)	0.64 (0.43-0.95)	0.71 (0.48-1.05)	0.66 (0.44-0.98)	0.42
KRAS-mutated*	1.0	0.89 (0.61-1.29)	0.66 (0.44-0.99)	0.75 (0.50-1.11)	0.71 (0.48-1.07)	0.47

Vitamin B_{12} (g)	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**	
			Nurses' Health Study			
Vitamin B_{12}, range (g)	**≤4.0**	**4.1-5.0**	**5.1-7.0**	**7.1-11.0**	**≥11.1**	
Cases / Person-years	75/374299	89/373459	62/373486	80/371351	85/369327	
All cancers‡	1.0	1.13 (0.83-1.54)	0.76 (0.54-1.06)	0.96 (0.70-1.32)	0.96 (0.70-1.30)	0.76
All cancers*	1.0	1.13 (0.83-1.54)	0.76 (0.54-1.06)	0.99 (0.72-1.36)	0.98 (0.71-1.34)	0.97
Cases / Person-years	55/374314	61/373484	42/373507	57/371369	57/369353	
KRAS-wildtype‡	1.0	0.95 (0.66-1.36)	0.70 (0.47-1.05)	0.94 (0.65-1.36)	0.87 (0.60-1.27)	0.94
KRAS-wildtype*	1.0	0.95 (0.66-1.37)	0.70 (0.47-1.05)	0.96 (0.66-1.40)	0.90 (0.62-1.30)	0.88
Cases / Person-years	20/374349	28/373505	20/373520	23/371398	28/369375	
KRAS-mutated‡	1.0	1.33 (0.75-2.37)	0.91 (0.49-1.70)	1.04 (0.57-1.89)	1.18 (0.66-2.09)	0.62
KRAS-mutated*	1.0	1.33 (0.75-2.36)	0.91 (0.49-1.70)	1.06 (0.58-1.94)	1.21 (0.68-2.15)	0.75
			Health Professionals Follow-up Study			
Vitamin B_{12}, range (g)	**≤6.0**	**6.1-8.0**	**8.1-11.0**	**11.1-16.0**	**≥16.1**	
Cases / Person-years	66/148898	42/148915	65/147747	51/146020	54/145974	
All cancers‡	1.0	0.64 (0.43-0.94)	0.95 (0.67-1.33)	0.68 (0.47-0.98)	0.74 (0.52-1.06)	0.74

All cancers[*]	1.0	0.58 (0.39-0.85)	0.86 (0.61-1.22)	0.62 (0.42-0.90)	0.67 (0.46-0.98)	0.76
Cases / Person-years	36/148898	22/148915	37/147747	27/146020	33/145974	
KRAS-wildtype[‡]	1.0	1.64 (0.96-2.78)	0.99 (0.63-1.57)	0.66 (0.40-1.09)	0.83 (0.52-1.33)	0.94
KRAS-wildtype[*]	1.0	1.80 (1.06-3.07)	0.90 (0.57-1.43)	0.60 (0.36-1.00)	0.76 (0.47-1.23)	0.96
Cases / Person-years	30/148898	20/148915	28/147747	24/146020	21/145974	
KRAS-mutated[‡]	1.0	0.67 (0.38-1.17)	0.90 (0.54-1.50)	0.70 (0.41-1.20)	0.63 (0.36-1.10)	0.64
KRAS-mutated[*]	1.0	0.60 (0.34-1.06)	0.81 (0.48-1.37)	0.63 (0.37-1.10)	0.57 (0.33-1.01)	0.63
			Both Cohorts Combined			
Cases / Person-years	141/516678	131/516089	127/514980	131/510819	139/508381	
All cancers[‡]	1.0	0.90 (0.71-1.14)	0.84 (0.66-1.07)	0.83 (0.65-1.05)	0.85 (0.67-1.08)	0.77
All cancers[*]	1.0	0.87 (0.69-1.11)	0.82 (0.64-1.04)	0.83 (0.65-1.06)	0.85 (0.67-1.08)	0.82
Cases / Person-years	91/516722	83/516134	79/515024	84/510856	90/508427	
KRAS-wildtype[‡]	1.0	1.13 (0.84-1.52)	0.81 (0.60-1.10)	0.83 (0.61-1.11)	0.85 (0.64-1.14)	0.87
KRAS-wildtype[*]	1.0	1.16 (0.86-1.57)	0.79 (0.58-1.07)	0.82 (0.61-1.11)	0.85 (0.63-1.14)	0.91
Cases / Person-years	50/516761	48/516160	48/515044	47/510894	49/508455	
KRAS-mutated[‡]	1.0	0.93 (0.63-1.38)	0.89 (0.60-1.33)	0.84 (0.56-1.25)	0.85 (0.57-1.25)	0.80
KRAS-mutated[*]	1.0	0.90 (0.61-1.34)	0.87 (0.58-1.30)	0.84 (0.56-1.25)	0.84 (0.57-1.25)	0.82

Alcohol (g)	**No alcohol**	**<5 g/day**	**5-14.9 g/day**	**≥15 g/day**	**P Trend**
		Nurses' Health Study			
Cases / Person-years	114/595225	146/629277	82/416136	49/221284	
All cancers[‡]	1.0	1.28 (1.00-1.64)	1.03 (0.78-1.37)	1.11 (0.80-1.55)	0.97
All cancers[*]	1.0	1.31 (1.03-1.69)	1.08 (0.80-1.44)	1.13 (0.80-1.59)	0.88
Cases / Person-years	81/595250	97/629325	56/416157	38/221295	
KRAS-wildtype[‡]	1.0	0.84 (0.62-1.12)	0.99 (0.71-1.39)	1.21 (0.83-1.78)	0.43
KRAS-wildtype[*]	1.0	0.81 (0.60-1.09)	1.03 (0.73-1.46)	1.23 (0.83-1.83)	0.51
Cases / Person-years	33/595294	49/629351	26/416184	11/221316	
KRAS-mutated[‡]	1.0	1.48 (0.95-2.31)	1.13 (0.67-1.88)	0.86 (0.44-1.70)	0.21
KRAS-mutated[*]	1.0	1.52 (0.98-2.38)	1.18 (0.70-1.97)	0.87 (0.44-1.74)	0.20
		Health Professionals Follow-up Study			
Cases / Person-years	60/172724	44/179417	79/201763	95/183650	

All cancers[‡]	1.0	0.75 (0.51-1.10)	1.17 (0.84-1.64)	1.48 (1.07-2.04)	0.003
All cancers[*]	1.0	0.74 (0.50-1.10)	1.14 (0.81-1.61)	1.44 (1.03-2.01)	0.01
Cases / Person-years	29/172724	26/179417	49/201763	51/183650	
KRAS-wildtype[‡]	1.0	1.10 (0.65-1.87)	1.51 (0.95-2.38)	1.64 (1.04-2.59)	0.08
KRAS-wildtype[*]	1.0	1.11 (0.65-1.88)	1.47 (0.92-2.33)	1.60 (1.00-2.55)	0.14
Cases / Person-years	31/172724	18/179417	30/201763	44/183650	
KRAS-mutated[‡]	1.0	0.59 (0.33-1.06)	0.86 (0.52-1.42)	1.32 (0.83-2.09)	0.009
KRAS-mutated[*]	1.0	0.59 (0.33-1.05)	0.84 (0.51-1.40)	1.29 (0.81-2.06)	0.02
	Both Cohorts Combined				
Cases / Person-years	174/759616	190/801009	161/609398	144/396923	
All cancers[‡]	1.0	1.10 (0.89-1.35)	1.12 (0.90-1.38)	1.38 (1.11-1.72)	0.01
All cancers[*]	1.0	1.12 (0.91-1.37)	1.12 (0.90-1.40)	1.33 (1.05-1.67)	0.07
Cases / Person-years	110/759666	123/801078	105/609450	89/396970	
KRAS-wildtype[‡]	1.0	0.89 (0.69-1.15)	1.15 (0.88-1.51)	1.35 (1.02-1.79)	0.10
KRAS-wildtype[*]	1.0	0.88 (0.68-1.13)	1.16 (0.89-1.52)	1.30 (0.97-1.74)	0.30
Cases / Person-years	64/759717	67/801107	56/609489	55/397001	
KRAS-mutated[‡]	1.0	1.05 (0.75-1.48)	1.05 (0.73-1.51)	1.42 (0.99-2.04)	0.03
KRAS-mutated[*]	1.0	1.07 (0.76-1.51)	1.06 (0.74-1.52)	1.37 (0.95-1.98)	0.08

[‡] Age-adjusted only.

[**] All models are adjusted for age (continuous), energy intake, gender, screening sigmoidoscopy, family history of colorectal cancer, aspirin use, smoking, physical activity in METs, baseline body mass index, a history of colon polyps, beef intake, calcium, multi-vitamin use, and baseline folate, vitamin B6, B12, methionine, and alcohol if not primary exposure.

KRAS mutation in codon 12 or 13.