

Table 1. Associations between *APC* codon 1822 genotypes and colorectal cancer and adenoma risk in the Nurses' Health Study, the Physicians' Health Study and the Health Professionals Follow-Up Study.

APC D1822V	Cases (%)*	Controls (%)*	Age Adjusted OR (95% CI)	Multivariate OR (95% CI)
NHS Cancer				
N	197	590		
Asp/Asp	112 (59.9)	269 (58.1)	1.00 (ref.)	1.00 (ref.) ¹
Asp/Val	62 (33.2)	169 (36.5)	0.87 (0.60 - 1.25)	0.83 (0.56 - 1.25)
Val/Val	13 (7.0)	25 (5.4)	1.26 (0.62 - 2.56)	1.18 (0.52 - 2.65)
Asp/Val +Val/Val	75 (40.1)	194 (41.9)	0.92 (0.65 - 1.30)	0.88 (0.60 - 1.29)
PHS Cancer				
N	274	456		
Asp/Asp	171 (64.3)	263 (60.2)	1.00 (ref.)	1.00 (ref.) ²
Asp/Val	80 (30.1)	143 (32.7)	0.82 (0.58 - 1.15)	0.83 (0.59 - 1.17)
Val/Val	15 (5.6)	31 (7.1)	0.75 (0.39 - 1.44)	0.73 (0.37 - 1.41)
Asp/Val +Val/Val	95 (35.7)	174 (39.8)	0.81 (0.59 - 1.11)	0.81 (0.59 - 1.12)
NHS Adenoma				
N	556	557		
Asp/Asp	301 (56.7)	303 (57.6)	1.00 (ref.)	1.00 (ref.) ³
Asp/Val	206 (38.8)	185 (35.2)	1.12 (0.87 - 1.45)	1.19 (0.91 - 1.56)
Val/Val	24 (4.5)	38 (7.2)	0.64 (0.37 - 1.09)	0.63 (0.36 - 1.11)
Asp/Val +Val/Val	230 (43.3)	223 (42.4)	1.04 (0.81 - 1.33)	1.09 (0.84 - 1.41)
HPFS Adenoma				
N	375	724		
Asp/Asp	226 (60.4)	437 (60.5)	1.00 (ref.)	1.00 (ref.) ⁴
Asp/Val	134 (35.8)	251 (34.8)	1.05 (0.80 - 1.37)	1.05 (0.79 - 1.39)
Val/Val	14 (3.7)	34 (4.7)	0.80 (0.42 - 1.53)	0.81 (0.41 - 1.60)
Asp/Val +Val/Val	230 (43.3)	223 (42.4)	1.02 (0.79 - 1.32)	1.09 (0.84 - 1.41)

1 Unconditional logistic regression adjusted for age, family history of colorectal cancer, smoking history, aspirin use, BMI, PMH use, physical activity, and intake of red meat, folate, and alcohol.

2. Unconditional logistic regression adjusted for age, smoking history, aspirin use, BMI, multivitamin use, and alcohol intake.

3 Unconditional logistic regression adjusted for age, year of endoscopy, family history of colorectal cancer, pack-years smoking, aspirin use, BMI, PMH use, physical activity, and intake of red meat, folate, and alcohol.

4 Unconditional logistic regression adjusted for age, history of previous endoscopy, year of endoscopy, family history of colorectal cancer, pack-years smoking, aspirin use, BMI, physical activity, and intake of red meat, folate, and alcohol.

* Numbers do not add to total due to missing genotype data.

Table 2. Associations between *APC* codon 2502 genotypes and colorectal cancer and adenoma risk in the Nurses' Health Study, the Physicians' Health Study and the Health Professionals Follow-Up Study.

APC Gly2502Ser	Cases (%)*	Controls (%)*	Age Adjusted OR (95% CI)	Multivariate OR (95% CI)
NHS Cancer				
N	197	590		
Gly/Gly	188 (95.9)	467 (96.5)	1.00 (ref.)	1.00 (ref.) ¹
Gly/Ser	8 (4.1)	17 (3.5)	1.19 (0.5 - 2.82)	1.17 (0.47 - 2.90)
PHS Cancer				
N	274	456		
Gly/Gly	258 (95.6)	433 (96.9)	1.00 (ref.)	1.00 (ref.) ²
Gly/Ser	12 (4.4)	14 (3.1)	1.39 (0.63 - 3.09)	1.47 (0.65 - 3.32)
NHS Adenoma				
N	556	557		
Gly/Gly	522 (97.4)	522 (96.7)	1.00 (ref.)	1.00 (ref.) ³
Gly/Ser	14 (2.6)	18 (3.3)	0.78 (0.38 - 1.59)	0.84 (0.40 - 1.76)
HPFS Adenoma				
N	375	724		
Gly/Gly	350 (95.1)	690 (96.8)	1.00 (ref.)	1.00 (ref.) ⁴
Gly/Ser	18 (4.9)	23 (3.2)	1.20 (0.39 - 3.70)	1.45 (0.76 - 2.75)

1 Unconditional logistic regression adjusted for age, family history of colorectal cancer, smoking history, aspirin use, BMI, PMH use, physical activity, and intake of red meat, folate, and alcohol.

2. Unconditional logistic regression adjusted for age, smoking history, aspirin use, BMI, multivitamin use, and alcohol intake.

3 Unconditional logistic regression adjusted for age, year of endoscopy, family history of colorectal cancer, pack-years smoking, aspirin use, BMI, PMH use, physical activity, and intake of red meat, folate, and alcohol.

4 Unconditional logistic regression adjusted for age, history of previous endoscopy, year of endoscopy, family history of colorectal cancer, pack-years smoking, aspirin use, BMI, physical activity, and intake of red meat, folate, and alcohol.

* Numbers do not add to total due to missing genotype data

Table 3. Relationship between lifestyle factors and colorectal adenoma risk stratified by *APC* Asp1822Val genotypes in the combined Nurses' Health Study and Health Professionals Follow-Up Study.

APC genotype		Asp/Asp	Asp/Val	Val/Val	<i>P</i> interaction
Pack-years of smoking ¹	0 years	1.00 (ref.) [207; 348] ⁴	1.18 (0.89 - 1.57) [140; 196]	0.38 (0.18 - 0.82) [9; 37]	0.46
	< 25 years	1.28 (0.98 - 1.69) [160; 208]	1.17 (0.85 - 1.6) [101; 139]	1.38 (0.7 - 2.70) [17; 21]	
	>= 25 years	1.56 (1.17 - 2.06) [157; 179]	1.85 (1.32 - 2.59) [98; 97]	1.27 (0.57 - 2.83) [12; 14]	
Alcohol Consumption (g/day) ^{1,2}	Low	1.00 (ref.) [152; 177]	0.81 (0.57 - 1.15) [90; 132]	0.6 (0.26 - 1.39) [9; 17]	0.37
	Med	0.86 (0.65 - 1.14) [240; 415]	1.06 (0.78 - 1.44) [165; 228]	0.6 (0.32 - 1.13) [16; 37]	
	High	1.16 (0.83 - 1.60) [132; 136]	1.26 (0.85 - 1.87) [78; 72]	0.82 (0.38 - 1.79) [12; 17]	
Aspirin intake ¹	Non-user	1.00 (ref.) [313; 406]	0.95 (0.74 - 1.21) [186; 257]	0.64 (0.36 - 1.14) [19; 37]	0.37
	User	0.75 (0.59 - 0.96) [194; 296]	0.89 (0.67 - 1.19) [130; 160]	0.57 (0.31 - 1.05) [17; 32]	
Family History ³	No	1.00 (ref.) [457; 665]	1.08 (0.89 - 1.31) [304; 403]	0.65 (0.42 - 1.01) [33; 68]	0.47
	Yes	1.24 (0.87 - 1.77) [69; 73]	1.38 (0.85 - 2.24) [37; 34]	1.75 (0.46 - 6.68) [5; 4]	

1 Unconditional logistic regression adjusted for age, family history of colorectal cancer, and sex.

2 NHS: low < 7.5, medium 7.5- 14, high >= 15; HPFS: low <= 15, medium 16 - 30, high > 30.

3 Unconditional logistic regression adjusted for age and sex.

4 [cases; controls]

Table 4. Relationship between fat intake and colorectal cancer risk stratified by *APC* Asp1822Val genotypes in the Nurses' Health Study.

APC Genotype		Asp/Asp	Asp/Val+Val/Val	<i>P</i> interaction
Total Fat ¹	High	1.00 (ref.) [56; 114] ²	0.88 (0.50 - 1.54) [35; 75]	0.92
	Low	0.77 (0.47 - 1.27) [49; 139]	0.70 (0.41 - 1.21) [35; 108]	
Saturated Fat ¹	High	1.00 (ref.) [49; 113]	1.24 (0.71 - 2.17) [40; 71]	0.10
	Low	0.94 (0.56 - 1.56) [56; 140]	0.61 (0.34 - 1.08) [30; 112]	
Polyunsaturated Fat ¹	High	1.00 (ref.) [55; 121]	0.91 (0.53 - 1.55) [37; 89]	0.90
	Low	0.95 (0.58 - 1.54) [50; 132]	0.82 (0.47 - 1.40) [33; 94]	
Monounsaturated Fat ¹	High	1.00 (ref.) [53; 122]	1.06 (0.61 - 1.84) [38; 77]	0.39
	Low	0.98 (0.59 - 1.61) [52; 131]	0.74 (0.42 - 1.28) [32; 106]	
Trans Fat ¹	High	1.00 (ref.) [53; 101]	0.94 (0.55 - 1.61) [42; 78]	0.66
	Low	0.67 (0.41 - 1.12) [52; 152]	0.53 (0.30 - 0.95) [28; 105]	

1 Unconditional logistic regression adjusted for age, family history of colorectal cancer, smoking history, aspirin use, BMI, PMH use, physical activity, and intake of red meat, folate, total calories and alcohol.

2 [cases; controls]

Table 5. Relationship between fat intake and colorectal adenoma risk stratified by *APC* Asp1822Val genotypes in the combined Nurses' Health Study and Health Professionals Follow-Up Study.

APC Genotype		Asp/Asp	Asp/Val	Val/Val	<i>P</i> interaction
Total Fat ¹	High	1.00 (ref.) [182; 247] ²	1.15 (0.84 - 1.57) [122; 142]	0.70 (0.34 - 1.46) [12; 23]	0.65
	Medium	0.92 (0.70 - 1.22) [164; 243]	0.94 (0.68 - 1.30) [99; 147]	0.65 (0.32 - 1.31) [13; 26]	
	Low	1.04 (0.79 - 1.38) [177; 237]	1.07 (0.78 - 1.47) [111; 141]	0.67 (0.32 - 1.41) [12; 22]	
Saturated Fat ¹	High	1.00 (ref.) [169; 257]	1.40 (1.02 - 1.92) [125; 131]	0.47 (0.21 - 1.08) [8; 25]	0.26
	Medium	1.12 (0.84 - 1.48) [174; 233]	1.03 (0.74 - 1.42) [98; 148]	1.10 (0.56 - 2.18) [16; 22]	
	Low	1.14 (0.86 - 1.51) [180; 237]	1.06 (0.77 - 1.45) [109; 151]	0.69 (0.34 - 1.41) [13; 24]	
Polyunsaturated Fat ¹	High	1.00 (ref.) [180; 243]	1.12 (0.81 - 1.53) [119; 146]	1.18 (0.55 - 2.50) [14; 16]	0.67
	Medium	1.02 (0.77 - 1.34) [181; 242]	0.97 (0.70 - 1.34) [101; 147]	0.34 (0.15 - 0.76) [8; 31]	
	Low	0.97 (0.73 - 1.28) [162; 242]	1.09 (0.79 - 1.50) [112; 137]	0.78 (0.39 - 1.55) [15; 24]	
Monounsaturated Fat ¹	High	1.00 (ref.) [184; 249]	1.06 (0.77 - 1.46) [113; 145]	0.87 (0.42 - 1.80) [13; 21]	0.93
	Medium	0.98 (0.74 - 1.29) [171; 244]	0.99 (0.72 - 1.35) [113; 158]	0.51 (0.24 - 1.07) [11; 26]	
	Low	1.03 (0.78 - 1.36) [168; 234]	1.17 (0.84 - 1.62) [106; 127]	0.72 (0.36 - 1.48) [13; 24]	
Trans Fat ¹	High	1.00 (ref.) [180; 248]	1.15 (0.84 - 1.58) [119; 137]	0.72 (0.35 - 1.47) [13; 24]	0.99
	Medium	1.02 (0.77 - 1.35) [175; 232]	0.86 (0.62 - 1.19) [93; 157]	0.73 (0.35 - 1.54) [12; 21]	
	Low	0.96 (0.72 - 1.27) [168; 247]	1.18 (0.86 - 1.61) [120; 136]	0.59 (0.29 - 1.22) [12; 26]	

¹ Unconditional logistic regression adjusted for age, sex, family history of colorectal cancer, and intake of total calories.

² [cases; controls]

Table 6. Relationship between postmenopausal hormone use and risk of colorectal cancer and adenoma among postmenopausal women in the Nurses' Health Study stratified by *APC* Asp1822Val genotypes.

APC genotype	PMH use		<i>P</i> Interaction
	never - past	current	
Cancer ¹			
Asp/Asp	1.00 (ref.) [57; 135]	0.84 (0.50 - 1.42) [39; 108]	0.02
Asp/Val	1.23 (0.72 - 2.12) [38; 73]	0.47 (0.24 - 0.93) [16; 74]	
Val/Val	2.82 (0.95 - 8.39) [9; 7]	0.42 (0.09 - 2.03) [3; 13]	
Asp/Val+Val/Val	1.38 (0.82 - 2.32) [47; 80]	0.46 (0.24 - 0.88) [19; 87]	0.03
Adenoma ²			
Asp/Asp	1.00 (ref.) [153; 128]	0.67 (0.46 - 0.96) [118; 148]	0.74
Asp/Val	1.23 (0.81 - 1.86) [93; 70]	0.87 (0.58 - 1.31) [94; 90]	
Val/Val	0.65 (0.30 - 1.40) [13; 18]	0.39 (0.15 - 1.01) [8; 18]	
Asp/Val+Val/Val	1.10 (0.74 - 1.62) [1106; 88]	0.80 (0.54 - 1.18) [102; 108]	0.74

1 Unconditional logistic regression adjusted for age, family history of colorectal cancer, smoking history, aspirin use, BMI, physical activity, and intake of red meat, folate, and alcohol.

2 Unconditional logistic regression adjusted for age, year of endoscopy, family history of colorectal cancer, pack-years smoking, aspirin use, BMI, physical activity, and intake of red meat, folate, and alcohol.

3 [cases; controls]

Supplementary Table 1. Relationship between lifestyle factors and colorectal cancer risk stratified by *APC* Asp1822Val genotypes in the Nurses' Health Study.

<i>APC</i> genotype		Asp/Asp	Asp/Val + Val/Val	<i>P</i> interaction
Pack-years of smoking before age 30 ¹	0 years	1.00 (ref.) [46; 126] ²	0.94 (0.54 - 1.62) [38; 94]	0.45
	< 10 years	1.13 (0.67 - 1.93) [49; 105]	1.07 (0.58 - 1.97) [29; 72]	
	>= 10 years	1.60 (0.74 - 3.44) [17; 26]	0.79 (0.29 - 2.16) [7; 20]	
Alcohol Consumption (g/day) ¹	<7.5	1.00 (ref.) [71; 191]	0.98 (0.63 - 1.53) [53; 138]	0.34
	>=7.5	1.42 (0.82 - 2.47) [34; 62]	0.91 (0.46 - 1.80) [17; 45]	
Aspirin intake ¹	Non-user	1.00 (ref.) [151; 129]	0.92 (0.51 - 1.65) [100; 93]	0.52
	1-6/wk	0.79 (0.44 - 1.40) [79; 81]	0.86 (0.46 - 1.62) [64; 62]	
	7+/wk	0.88 (0.43 - 1.80) [52; 56]	0.49 (0.22 - 1.12) [39; 45]	
Family History ¹	No	1.00 (ref.) [105; 253]	0.88 (0.59 - 1.30) [4; 14]	0.87
	Yes	0.60 (0.18 - 1.96) [71; 182]	0.44 (0.09 - 2.23) [2; 10]	

1 Unconditional logistic regression adjusted for age, family history of colorectal cancer, smoking history, aspirin use, BMI, PMH use, physical activity, and intake of red meat, folate, and alcohol.
2 [cases; controls]

Supplementary Table 2. Relationship between lifestyle factors and colorectal cancer risk stratified by *APC* Asp1822Val genotypes in the Physicians' Health Study.

<i>APC</i> genotype		Asp/Asp	Asp/Val + Val/Val	<i>P</i> interaction
Smoking History ¹	Never	1.00 (ref.) [64; 103] ²	0.74 (0.44 - 1.24) [35; 74]	0.28
	Past	1.04 (0.68 - 1.60) [92; 136]	0.73 (0.45 - 1.19) [49; 94]	
	Current	0.87 (0.42 - 1.80) [15; 28]	1.78 (0.71 - 4.49) [11; 12]	
Alcohol Consumption (g/day) ¹	<15	1.00 (ref.) [117; 183]	0.74 (0.50 - 1.10) [64; 129]	0.58
	>=15	0.96 (0.63 - 1.47) [54; 82]	0.87 (0.51 - 1.46) [31; 50]	
Aspirin intake ¹	Non-user	1.00 (ref.) [80; 136]	0.90 (0.57 - 1.42) [51; 91]	0.40
	User	1.18 (0.80 - 1.75) [91; 131]	0.81 (0.51 - 1.29) [44; 89]	
Family History ¹	No	1.00 (ref.) [150; 235]	0.78 (0.55 - 1.10) [81; 160]	0.78
	Yes	1.13 (0.61 - 2.07) [21; 32]	1.00 (0.48 - 2.08) [14; 20]	

1. Unconditional logistic regression adjusted for age, smoking history, aspirin use, BMI, multivitamin use, and alcohol intake.

2 [cases; controls]

Supplementary Table 3. Relationship between fat intake and colorectal adenoma risk stratified by *APC* Asp1822Val genotypes in the combined Nurses' Health Study and Health Professionals Follow-Up Study.

APC Genotype		Asp/Asp	Asp/Val	Val/Val	<i>P</i> interaction
Folate (mcg) with supplement ¹					0.35
	Low	1.00 (ref.) [162; 238] ²	1.19 (0.86 - 1.66) [107; 127]	0.67 (0.31 - 1.42) [11; 23]	
	Med	1.11 (0.84 - 1.48) [181; 233]	0.97 (0.70 - 1.35) [101; 150]	1.20 (0.53 - 2.71) [12; 14]	
	High	0.98 (0.74 - 1.29) [181; 257]	1.12 (0.82 - 1.53) [124; 154]	0.53 (0.27 - 1.03) [14; 34]	
Red Meat ¹					0.35
	Low	1.00 (ref.) [272; 385]	0.95 (0.74 - 1.23) [163; 240]	0.70 (0.40 - 1.23) [21; 39]	
	High	1.03 (0.82 - 1.30) [255; 355]	1.28 (0.99 - 1.66) [177; 196]	0.72 (0.39 - 1.33) [17; 33]	
BMI (quintiles) ¹					0.92
	1	1.00 (ref.) [90; 139]	1.14 (0.74 - 1.76) [60; 81]	0.82 (0.36 - 1.88) [10; 18]	
	2	0.99 (0.70 - 1.40) [135; 203]	1.02 (0.69 - 1.51) [81; 116]	0.80 (0.34 - 1.91) [9; 17]	
	3	1.22 (0.86 - 1.73) [145; 180]	1.39 (0.95 - 2.03) [106; 112]	0.51 (0.21 - 1.21) [8; 21]	
	4	1.31 (0.88 - 1.97) [77; 106]	1.29 (0.81 - 2.05) [49; 68]	0.97 (0.31 - 3.05) [5; 9]	
	5	1.45 (0.95 - 2.21) [66; 94]	1.4 (0.84 - 2.34) [35; 53]	1.61 (0.52 - 5.05) [6; 7]	
METS ¹					0.86
	Low	1.00 (ref.) [160; 211]	1.11 (0.79 - 1.58) [93; 112]	0.62 (0.29 - 1.32) [11; 23]	
	Med	0.87 (0.65 - 1.16) [176; 253]	0.99 (0.72 - 1.37) [116; 149]	0.82 (0.41 - 1.66) [15; 21]	
	High	0.91 (0.69 - 1.21) [191; 276]	0.93 (0.68 - 1.27) [131; 175]	0.53 (0.26 - 1.08) [12; 28]	
Total Calories ¹					0.88
	Low	1.00 (ref.) [277; 388]	1.03 (0.80 - 1.33) [174; 225]	0.73 (0.39 - 1.36) [17; 31]	
	High	1.02 (0.82 - 1.29) [247; 340]	1.13 (0.87 - 1.46) [158; 206]	0.66 (0.37 - 1.16) [20; 40]	

1 Unconditional logistic regression adjusted for age, family history of colorectal cancer, and sex.

2 [cases; controls]