

Table 1. Associations between XRCC genotypes and colorectal adenoma risk in the Nurses' Health Study and the Health Professionals Follow-Up Study.

Genotype	Health Professionals Follow-Up Study (HPFS)			Nurses' Health Study (NHS)			HPFS + NHS		
	Cases (%)	Controls (%)	OR (95% CI) ¹	Cases (%)	Controls (%)	OR (95% CI) ¹	Cases (%)	Controls (%)	OR (95% CI) ²
N	376 (34.2)	725 (65.8)		556 (50.0)	557 (50.0)		932 (42.1)	1282 (57.9)	
XRCC2 R188H									
Arg/Arg	302 (85.3)	582 (84.6)	1.00 (ref.)	450 (86.9)	441 (84.5)	1.00 (ref.)	751 (86.2)	1021 (84.5)	1.00 (ref.)
Arg/His + His/His	52 (14.7)	106 (15.4)	0.96 (0.65 - 1.42)	68 (13.1)	81 (15.5)	0.81 (0.56 - 1.18)	120 (13.8)	187 (15.5)	0.88 (0.68 - 1.13)
XRCC3 A>G 4541									
A/A	229 (62.9)	467 (65.8)	1.00 (ref.)	365 (66.6)	342 (62.6)	1.00 (ref.)	593 (65.1)	808 (64.4)	1.00 (ref.)
A/G	119 (32.7)	223 (31.4)	1.06 (0.79 - 1.43)	167 (30.5)	180 (33.0)	0.87 (0.66 - 1.16)	286 (31.4)	402 (32.1)	0.98 (0.81 - 1.18)
G/G	16 (4.4)	20 (2.8)	1.73 (0.84 - 3.56)	16 (2.9)	24 (4.4)	0.65 (0.31 - 1.34)	32 (3.5)	44 (3.5)	0.97 (0.61 - 1.57)
XRCC3 A>G 17893									
A/A	180 (49.2)	329 (46.7)	1.00 (ref.)	256 (48.7)	250 (47.5)	1.00 (ref.)	436 (48.9)	578 (47.0)	1.00 (ref.)
A/G	155 (42.4)	303 (43.0)	0.89 (0.66 - 1.20)	212 (40.3)	222 (42.2)	0.87 (0.65 - 1.17)	366 (41.1)	524 (42.6)	0.93 (0.77 - 1.12)
G/G	31 (8.5)	73 (10.4)	0.87 (0.52 - 1.48)	58 (11.0)	54 (10.3)	1.00 (0.65 - 1.54)	89 (10.0)	127 (10.4)	0.90 (0.67 - 1.22)
XRCC3 T241M									
Thr/Thr	140 (39.6)	257 (37.4)	1.00 (ref.)	191 (39.6)	187 (39.4)	1.00 (ref.)	331 (39.6)	442 (38.1)	1.00 (ref.)
Thr/Met	164 (46.3)	322 (46.8)	0.90 (0.66 - 1.22)	222 (46.1)	218 (45.9)	1.11 (0.82 - 1.52)	385 (46.1)	540 (46.5)	0.95 (0.78 - 1.16)
Met/Met	50 (14.1)	109 (15.8)	0.87 (0.57 - 1.33)	69 (14.3)	70 (14.8)	1.03 (0.66 - 1.63)	119 (14.3)	179 (15.4)	0.89 (0.68 - 1.17)

1 Conditional logistic regression adjusted for matching factors and family history of colorectal cancer, pack-years smoking, aspirin use, BMI, PMH use (NHS), and intake of folic acid and alcohol.

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

Appendix 1. Relationship of smoking to colorectal adenoma risk stratified by XRCC genotypes in the Health Professionals Follow-Up Study.

Genotype	Packyears Smoking		
	0 years	< 25 years	>= 25 years
XRCC2 R188H			
Arg/Arg	1.00 (ref.) ¹ [105; 268] ²	1.42 (0.99, 2.03) [96; 162]	1.72 (1.17, 2.52) [90; 124]
Arg/His + His/His	1.13 (0.65, 1.98) [23; 50]	1.34 (0.66, 2.74) [15; 26]	0.90 (0.39, 2.06) [10; 24]
			LRT p-value = 0.31
XRCC3 A>G 4541			
A/A	1.00 (ref.) [83; 212]	1.15 (0.76, 1.74) [66; 132]	1.69 (1.10, 2.59) [70; 97]
A/G	0.93 (0.59, 1.47) [40; 109]	1.78 (1.08, 2.93) [42; 59]	1.54 (0.88, 2.69) [31; 46]
G/G	1.52 (0.47, 4.87) [5; 8]	2.41 (0.66, 8.78) [5; 5]	2.42 (0.77, 7.62) [6; 7]
			LRT p-value = 0.63
XRCC3 A>G 17893			
A/A	1.00 (ref.) [68; 155]	1.37 (0.86, 2.16) [53; 90]	1.60 (0.99, 2.58) [55; 72]
A/G	0.81 (0.52, 1.27) [49; 142]	1.19 (0.74, 1.93) [52; 84]	1.54 (0.91, 2.62) [42; 58]
G/G	1.07 (0.54, 2.15) [15; 32]	0.85 (0.34, 2.18) [7; 20]	1.06 (0.43, 2.66) [8; 17]
			LRT p-value = 0.80
XRCC3 T241M			
Thr/Thr	1.00 (ref.) [47; 121]	1.57 (0.91, 2.69) [46; 71]	1.88 (1.07, 3.31) [39; 54]
Thr/Met	1.12 (0.7, 1.79) [59; 147]	1.32 (0.79, 2.21) [47; 89]	1.81 (1.05, 3.10) [53; 70]
Met/Met	1.10 (0.59, 2.06) [22; 51]	1.38 (0.67, 2.84) [16; 30]	1.08 (0.47, 2.46) [11; 23]
			LRT p-value = 0.74

1 Unconditional logistic regression adjusted for age, previous endoscopy, year of endoscopy, family history of colorectal cancer, aspirin use, BMI, physical activity, and intake of red meat, folic acid, and alcohol.

2 [cases; controls]

Appendix 2. Relationship of smoking to colorectal adenoma risk stratified by XRCC genotypes in the Nurses' Health Study.

Genotype	Packyears Smoking		
	0 years	< 25 years	>= 25 years
XRCC2 R188H			
Arg/Arg	1.00 (ref.) ¹ [186; 199] ²	1.07 (0.77 - 1.49) [143; 142]	1.48 (1.02 - 2.15) [116; 91]
Arg/His + His/His	0.73 (0.42 - 1.26) [26; 42]	1.05 (0.58 - 1.91) [25; 29]	2.06 (0.90 - 4.73) [17; 10]
			LRT p-value = 0.43
XRCC3 A>G 4541			
A/A	1.00 (ref.) [149; 154]	1.13 (0.79 - 1.62) [122; 113]	1.44 (0.95 - 2.19) [91; 69]
A/G	0.86 (0.58 - 1.29) [72; 90]	0.93 (0.58 - 1.52) [47; 53]	1.43 (0.85 - 2.40) [46; 33]
G/G	0.68 (0.24 - 1.93) [7; 9]	0.24 (0.05 - 1.17) [2; 9]	1.40 (0.42 - 4.66) [7; 6]
			LRT p-value = 0.61
XRCC3 A>G 17893			
A/A	1.00 (ref.) [101; 126]	1.31 (0.85 - 2.03) [83; 76]	2.04 (1.25 - 3.32) [70; 46]
A/G	1.13 (0.75 - 1.70) [91; 95]	1.04 (0.67 - 1.63) [62; 77]	1.66 (1.00 - 2.76) [56; 42]
G/G	1.66 (0.90 - 3.08) [32; 24]	1.07 (0.50 - 2.32) [15; 17]	1.24 (0.51 - 3.04) [11; 13]
			LRT p-value = 0.36
XRCC3 T241M			
Thr/Thr	1.00 (ref.) [89; 83]	0.75 (0.45 - 1.24) [50; 63]	1.38 (0.80 - 2.38) [51; 39]
Thr/Met	0.84 (0.54 - 1.29) [90; 103]	1.12 (0.70 - 1.80) [79; 70]	1.40 (0.80 - 2.47) [51; 38]
Met/Met	0.71 (0.39 - 1.30) [27; 35]	0.79 (0.39 - 1.58) [20; 24]	1.83 (0.79 - 4.29) [21; 11]
			LRT p-value = 0.41

1 Unconditional logistic regression adjusted for age, previous endoscopy, year of endoscopy, family history of colorectal cancer, aspirin use, BMI, PMH use, physical activity, and intake of red meat, folic acid, and alcohol.

2 [cases; controls]

Appendix 3. Relationship of alcohol consumption to colorectal adenoma risk stratified by XRCC genotypes in the Health Professionals Follow-Up Study.

Genotype	Alcohol Consumption (g/day)		
	<=5	5-30	>=30
XRCC2 R188H			
Arg/Arg	1.00 (ref.) ¹ [118; 253] ²	0.90 (0.65, 1.26) [125; 264]	1.77 (1.12, 2.80) [59; 65]
Arg/His + His/His	0.61 (0.31, 1.20) [14; 48]	1.08 (0.63, 1.86) [31; 50]	1.39 (0.46, 4.21) [7; 8]
			LRT p-value = 0.30
XRCC3 A>G 4541			
A/A	1.00 (ref.) [81; 209]	1.12 (0.77, 1.63) [106; 205]	1.84 (1.09, 3.11) [42; 53]
A/G + G/G	1.29 (0.83, 2.02) [53; 103]	1.11 (0.71, 1.74) [57; 115]	2.12 (1.09, 4.12) [25; 25]
			LRT p-value = 0.71
XRCC3 A>G 17893			
A/A	1.00 (ref.) [69; 160]	1.44 (0.95, 2.2) [83; 133]	1.81 (0.99, 3.31) [28; 36]
A/G	1.10 (0.69, 1.74) [51; 124]	0.90 (0.58, 1.39) [69; 147]	2.27 (1.22, 4.23) [35; 32]
G/G	1.55 (0.73, 3.29) [15; 26]	0.78 (0.39, 1.6) [13; 39]	0.88 (0.22, 3.51) [3; 8]
			LRT p-value = 0.09
XRCC3 T241M			
Thr/Thr	1.00 (ref.) [53; 106]	0.86 (0.53, 1.40) [65; 127]	1.55 (0.74, 3.24) [22; 24]
Thr/Met	0.87 (0.54, 1.41) [59; 144]	0.9 (0.56, 1.44) [67; 138]	1.67 (0.91, 3.06) [38; 40]
Met/Met	0.62 (0.32, 1.19) [17; 56]	1 (0.54, 1.85) [27; 45]	1.53 (0.47, 4.99) [6; 8]
			LRT p-value = 0.74

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

2 [cases; controls]

Appendix 4. Relationship of alcohol consumption to colorectal adenoma risk stratified by XRCC genotypes in the Nurses' Health Study.

Genotype	Alcohol Consumption (g/day)		
	0	<5.7	>=5.7
XRCC2 R188H			
Arg/Arg	1.00 (ref.) ¹ [155; 159] ²	1.06 (0.76 - 1.49) [147; 141]	1.09 (0.76 - 1.57) [137; 124]
Arg/His + His/His	1.12 (0.64 - 1.97) [31; 31]	0.98 (0.52 - 1.84) [22; 27]	0.69 (0.32 - 1.48) [14; 21]
			LRT p-value = 0.49
XRCC3 A>G 4541			
A/A	1.00 (ref.) [124; 130]	1.22 (0.84 - 1.77) [125; 109]	1.19 (0.79 - 1.79) [106; 91]
A/G	1.13 (0.72 - 1.76) [67; 64]	0.86 (0.54 - 1.38) [48; 58]	0.97 (0.60 - 1.58) [50; 53]
G/G	1.76 (0.49 - 6.36) [7; 4]	0.33 (0.10 - 1.08) [4; 11]	0.58 (0.18 - 1.89) [5; 8]
			LRT p-value = 0.18
XRCC3 A>G 17893			
A/A	1.00 (ref.) [92; 80]	0.89 (0.57 - 1.39) [83; 81]	0.78 (0.49 - 1.24) [76; 78]
A/G	0.81 (0.52 - 1.27) [84; 90]	0.72 (0.44 - 1.16) [59; 70]	1.01 (0.61 - 1.68) [63; 57]
G/G	0.94 (0.44 - 2.01) [17; 17]	1.14 (0.57 - 2.25) [25; 20]	0.76 (0.34 - 1.70) [15; 16]
			LRT p-value = 0.50
XRCC3 T241M			
Thr/Thr	1.00 (ref.) [75; 70]	1.07 (0.65 - 1.75) [70; 63]	0.84 (0.48 - 1.47) [43; 48]
Thr/Met	1.04 (0.64 - 1.69) [76; 74]	1.02 (0.62 - 1.69) [66; 64]	1.00 (0.61 - 1.66) [73; 70]
Met/Met	1.04 (0.54 - 1.99) [29; 26]	0.94 (0.49 - 1.82) [26; 26]	0.65 (0.27 - 1.52) [13; 16]
			LRT p-value = 0.93

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

2 [cases; controls]

Appendix 5. Relationship of folate consumption to colorectal adenoma risk stratified by XRCC genotypes in the Health Professionals Follow-Up Study.

Genotype	Folate Consumption (mcg/day)		
	<=338	339-496	>=497
XRCC2 R188H			
Arg/Arg	1.00 (ref.) ¹ [200; 99] ²	0.99 (0.69 - 1.43) [188; 100]	0.97 (0.67 - 1.4) [194; 103]
Arg/His + His/His	0.65 (0.31 - 1.34) [35; 15]	1.08 (0.57 - 2.05) [35; 19]	0.94 (0.47 - 1.87) [36; 18]
			LRT p-value = 0.55
XRCC3 A>G 4541			
A/A	1.00 (ref.) [153; 76]	0.94 (0.62 - 1.43) [158; 79]	0.84 (0.55 - 1.28) [156; 74]
A/G + G/G	0.94 (0.58 - 1.53) [86; 44]	1.01 (0.61 - 1.66) [76; 42]	1.23 (0.75 - 2) [81; 49]
			LRT p-value = 0.44
XRCC3 A>G 17893			
A/A	1.00 (ref.) [103; 52]	1.21 (0.75 - 1.95) [109; 65]	1.08 (0.67 - 1.75) [117; 63]
A/G	1.07 (0.64 - 1.77) [103; 56]	0.97 (0.58 - 1.62) [99; 51]	0.83 (0.49 - 1.41) [101; 48]
G/G	0.81 (0.36 - 1.86) [28; 10]	0.53 (0.21 - 1.34) [28; 8]	1.65 (0.72 - 3.79) [17; 13]
			LRT p-value = 0.24
XRCC3 T241M			
Thr/Thr	1.00 (ref.) [96; 40]	1.1 (0.63 - 1.92) [86; 45]	1.73 (1 - 3.01) [75; 55]
Thr/Met	1.36 (0.8 - 2.3) [102; 58]	1.25 (0.74 - 2.1) [108; 56]	1.03 (0.6 - 1.76) [112; 50]
Met/Met	0.86 (0.38 - 1.93) [35; 12]	1.64 (0.82 - 3.28) [33; 21]	0.85 (0.42 - 1.75) [41; 17]
			LRT p-value = 0.08

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

2 [cases; controls]

Appendix 6. Relationship of folate consumption to colorectal adenoma risk stratified by XRCC genotypes in the Nurses' Health Study.

Genotype	Folate Consumption (mcg/day)		
	<=310	311-507	>=508
XRCC2 R188H			
Arg/Arg	1.00 (ref.) ¹ [128; 129] ²	1.16 (0.81 - 1.66) [144; 128]	1.12 (0.79 - 1.58) [166; 166]
Arg/His + His/His	2.02 (1.01 - 4.03) [27; 16]	0.83 (0.43 - 1.58) [20; 28]	0.67 (0.36 - 1.26) [20; 35]
			LRT p-value = 0.26
XRCC3 A>G 4541			
A/A	1.00 (ref.) [112; 99]	1.09 (0.73 - 1.63) [120; 98]	0.89 (0.61 - 1.31) [123; 133]
A/G + G/G	0.79 (0.48 - 1.28) [50; 55]	0.78 (0.49 - 1.25) [55; 63]	0.90 (0.58 - 1.38) [76; 80]
			LRT p-value = 0.50
XRCC3 A>G 17893			
A/A	1.00 (ref.) [74; 71]	1.08 (0.68 - 1.72) [84; 79]	1.09 (0.69 - 1.72) [93; 89]
A/G	1.17 (0.71 - 1.93) [66; 58]	0.97 (0.59 - 1.60) [64; 64]	0.88 (0.55 - 1.39) [76; 95]
G/G	0.74 (0.34 - 1.62) [15; 19]	1.87 (0.89 - 3.94) [25; 15]	1.03 (0.48 - 2.19) [17; 19]
			LRT p-value = 0.53
XRCC3 T241M			
Thr/Thr	1.00 (ref.) [54; 52]	1.06 (0.61 - 1.85) [60; 56]	1.07 (0.63 - 1.81) [74; 73]
Thr/Met	1.07 (0.63 - 1.82) [72; 66]	1.19 (0.69 - 2.06) [67; 59]	1.07 (0.64 - 1.81) [76; 83]
Met/Met	1.12 (0.52 - 2.39) [21; 19]	0.78 (0.39 - 1.57) [23; 28]	1.06 (0.51 - 2.20) [24; 21]
			LRT p-value = 0.47

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

2 [cases; controls]

Appendix 7. Relationship of plasma folate to colorectal adenoma risk stratified by XRCC genotypes in the Nurses' Health Study.

Genotype	Plasma Folate (quartiles)			
	1	2	3	4
XRCC2 R188H				
Arg/Arg	1.00 (ref.) ¹ [57; 46] ²	0.94 (0.53 - 1.65) [71; 64]	1.00 (0.57 - 1.76) [80; 71]	0.86 (0.49 - 1.52) [77; 76]
Arg/His + His/His	0.70 (0.21 - 2.32) [6; 9]	0.55 (0.21 - 1.44) [9; 18]	0.76 (0.29 - 1.98) [11; 12]	0.78 (0.29 - 2.11) [10; 13]
				LRT p-value = 0.60
XRCC3 A>G 4541				
A/A	1.00 (ref.) [42; 34]	0.77 (0.41 - 1.44) [59; 61]	0.86 (0.45 - 1.65) [55; 54]	0.92 (0.48 - 1.73) [67; 58]
A/G + G/G	0.87 (0.4 - 1.88) [26; 23]	0.77 (0.35 - 1.72) [23; 26]	0.94 (0.46 - 1.9) [42; 34]	0.60 (0.28 - 1.28) [27; 34]
				LRT p-value = 0.58
XRCC3 A>G 17893				
A/A	1.00 (ref.) [35; 31]	0.94 (0.45 - 2.01) [33; 31]	0.99 (0.49 - 2.01) [44; 43]	0.97 (0.47 - 2.02) [42; 36]
A/G + G/G	1.21 (0.55 - 2.66) [32; 24]	0.84 (0.42 - 1.68) [44; 51]	1.16 (0.57 - 2.35) [50; 39]	0.81 (0.4 - 1.64) [45; 52]
				LRT p-value = 0.66
XRCC3 T241M				
Thr/Thr	1.00 (ref.) [28; 27]	0.73 (0.32 - 1.67) [24; 32]	1.77 (0.74 - 4.22) [30; 18]	1.43 (0.65 - 3.14) [40; 30]
Thr/Met + Met/Met	1.28 (0.56 - 2.91) [34; 27]	1.33 (0.64 - 2.76) [51; 43]	1.01 (0.49 - 2.11) [49; 53]	0.94 (0.43 - 2.02) [37; 42]
				LRT p-value = 0.07

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

2 [cases; controls]