

**Web Table 1. Direct and indirect effects on lung cancer and assessment of variant-smoking interaction for rs8034191**

	Original Study		Replication				Toronto			Meta-Analysis	
	MGH		MD Anderson		IARC				Overall Replication		
	OR	P-Value	OR	P-Value	OR	P-Value	OR	P-Value	P-Value	Pooled OR	P-Val
<b>w/o SNPxSmoking Interaction</b>											
Direct Effect	1.35 (1.21,1.52)	3.1x10 <sup>-7</sup>	1.18 (1.08, 1.29)	2.0x10 <sup>-4</sup>	1.26 (1.14,1.40)	5.4x10 <sup>-6</sup>	1.33 (1.02,1.73)	0.04	4.7x10 <sup>-10</sup>	1.26 (1.19,1.33)	1.8x
Indirect Effect	1.01 (0.99,1.02)	0.15	1.01 (0.99,1.03)	0.13	1.00 (0.99,1.02)	0.95	1.00 (0.99,1.01)	0.87	0.23	1.01 (1.00,1.01)	
Total Effect	1.36 (1.22,1.54)	1.5x10 <sup>-7</sup>	1.19 (1.09,1.30)	8.8x10 <sup>-5</sup>	1.26 (1.14,1.40)	6.4x10 <sup>-6</sup>	1.33 (1.02,1.74)	0.03	2.6x10 <sup>-10</sup>	1.26 (1.19,1.34)	6.7x
Proportion Mediated		3.6%		6.8%		0.2%		0.4%			3.2%
<b>w/ SNPxSmoking Interaction</b>											
T/C vs. TT Direct Effect	1.31 (1.15,1.49)	3.1x10 <sup>-5</sup>	1.08 (0.97,1.21)	0.15	1.24 (1.11,1.38)	1.8x10 <sup>-4</sup>	1.30 (0.99,1.71)	0.06	8.4x10 <sup>-5</sup>	1.20 (1.12,1.28)	5.6
T/C vs. TT Indirect Effect	1.01 (0.99,1.02)	0.15	1.01 (0.99,1.03)	0.13	1.00 (0.99,1.02)	0.95	1.00 (0.99,1.01)	0.78	0.22	1.01 (1.00,1.01)	
T/C vs. TT Total Effect	1.32 (1.16,1.50)	1.6x10 <sup>-5</sup>	1.10 (0.98,1.23)	0.10	1.24 (1.11,1.39)	2.0x10 <sup>-4</sup>	1.30 (-.99,1.71)	0.06	4.8x10 <sup>-5</sup>	1.21 (1.13,1.29)	1.9
Proportion Mediated		4.2%		13.0%		0.3%		0.7%			4.2%
C/C vs. TT Direct Effect	1.72 (1.34,2.21)	2.1x10 <sup>-5</sup>	1.18 (0.96,1.47)	0.11	1.53 (1.23,1.92)	1.5x10 <sup>-4</sup>	1.70 (0.99,2.93)	0.06	4.8x10 <sup>-5</sup>	1.44 (1.27,1.63)	2.3
C/C vs. TT Indirect Effect	1.03 (0.99,1.07)	0.16	1.03 (0.99,1.07)	0.13	1.00 (0.97,1.04)	0.95	1.00 (0.97,1.05)	0.61	0.2	1.02 (1.00,1.04)	
C/C vs. TT Total Effect	1.77 (1.38,2.26)	6.7x10 <sup>-6</sup>	1.22 (0.98,1.51)	0.07	1.54 (1.23,1.92)	1.7x10 <sup>-4</sup>	1.72 (1.00,2.94)	0.05	2.1x10 <sup>-5</sup>	1.46 (1.29,1.66)	4.4
Proportion Mediated		6.3%		15.2%		0.3%		2.3%			5.6%
Additive Interaction	0.06 (0.02,0.10)	1x10 <sup>-3</sup>	0.05 (0.03,0.08)	1.8x10 <sup>-5</sup>	0.07 (0.03,0.10)	1.0x10 <sup>-4</sup>	0.04 (-0.06,0.15)	0.48	5.6x10 <sup>-8</sup>	0.06 (0.04,0.08)	2.3x
Multiplicative Interaction	1.04 (0.98,1.09)	0.17	1.05 (1.01,1.09)	0.01	1.03 (0.96,1.09)	0.42	1.04 (0.93,1.15)	0.51	0.03	1.04 (1.01,1.07)	

**Web Table 2. Direct and indirect effects on lung cancer and assessment of variant-smoking interaction for rs1051730**

	Original Study		Replication				Meta-Analysis				
	MGH		MD Anderson		IARC		Toronto		Overall		
	OR	P-Value	OR	P-Value	OR	P-Value	OR	P-Value	Replication	Pooled	P-Val
<b>w/o SNPxSmoking Interaction</b>											
Direct Effect	1.32 (1.18,1.48)	1.8x10 <sup>-6</sup>	1.19 (1.09,1.30)	1.0x10 <sup>-4</sup>	1.27 (1.14,1.40)	4.1x10 <sup>-6</sup>	1.42 (1.09,1.86)	0.01	7.7x10 <sup>-11</sup>	1.26 (1.19,1.33)	1.1x
Indirect Effect	1.01 (0.99,1.02)	0.19	1.01 (0.99,1.02)	0.26	1.00 (0.98,1.01)	0.87	1.00 (0.99,1.01)	0.82	0.45	1.00 (0.99,1.01)	
Total Effect	1.33 (1.19,1.50)	1.0x10 <sup>-6</sup>	1.20 (1.10,1.31)	5.8x10 <sup>-5</sup>	1.27 (1.14,1.40)	5.9x10 <sup>-6</sup>	1.42 (1.09,1.86)	0.01	5.6x10 <sup>-11</sup>	1.26 (1.19,1.34)	4.4x
Proportion Mediated	3.5%		4.9%		0.0%		0.4%			2.3%	
<b>w/ SNPxSmoking Interaction</b>											
A/G vs. GG Direct Effect	1.29 (1.14,1.46)	7.6x10 <sup>-5</sup>	1.09 (0.98,1.22)	0.12	1.24 (1.10,1.38)	2.0x10 <sup>-4</sup>	1.41 (1.07,1.87)	0.01	3.4x10 <sup>-5</sup>	1.20 (1.12,1.28)	3.7:
A/G vs. GG Indirect Effect	1.01 (0.99,1.02)	0.19	1.01 (0.99,1.02)	0.26	1.00 (0.98,1.01)	0.87	1.00 (0.99,1.01)	0.81	0.45	1.01 (0.99,1.01)	
A/G vs. GG Total Effect	1.30 (1.15,1.47)	4.2x10 <sup>-5</sup>	1.10 (0.98,1.23)	0.09	1.24 (1.10,1.38)	2.7x10 <sup>-4</sup>	1.42 (1.07,1.87)	0.01	1.8x10 <sup>-5</sup>	1.21 (1.13,1.29)	1.2:
Proportion Mediated	4.1%		9.3%		0.0%		0.5%			3.0%	
A/A vs. GG Direct Effect	1.66 (1.30,2.12)	5.8x10 <sup>-5</sup>	1.20 (0.97,1.48)	0.10	1.53 (1.22,1.91)	1.8x10 <sup>-4</sup>	2.00 (1.15,3.48)	0.01	1.8x10 <sup>-5</sup>	1.44 (1.27,1.64)	1.4:
A/A vs. GG Indirect Effect	1.02 (0.99,1.06)	0.20	1.02 (0.98,1.06)	0.26	1.00 (0.96,1.03)	0.88	1.00 (0.97,1.04)	0.82	0.43	1.01 (0.99,1.03)	
A/A vs. GG Total Effect	1.70 (1.33,1.17)	2.3x10 <sup>-5</sup>	1.22 (0.99,1.51)	0.07	1.53 (1.22,1.91)	2.4x10 <sup>-4</sup>	2.01 (1.16,3.47)	0.01	1.2x10 <sup>-5</sup>	1.46 (1.29,1.66)	5.1:
Proportion Mediated	5.7%		11.1%		0.0%		0.7%			4.0%	
Additive Interaction	0.05 (0.02,0.09)	4x10 <sup>-3</sup>	0.05 (0.03,0.08)	1.8x10 <sup>-5</sup>	0.07 (0.04,0.11)	6.0x10 <sup>-5</sup>	0.01 (-0.10,0.13)	0.85	1.1x10 <sup>-7</sup>	0.06 (0.04,0.08)	1.4:
Multiplicative Interaction	1.03 (0.98,1.08)	0.26	1.05 (1.01, 1.09)	0.01	1.03 (0.97,1.10)	0.34	1.01 (0.90,1.12)	0.95	0.03	1.04 (1.00,1.07)	