Table I. Summary statistics of subjects included in the interaction analysis. Percentages are reported for cases and control groups.

		CENTRE						Overall sample	
		Casale Monferrato		Genova		Torino			
		controls	cases	controls	cases	controls	cases	controls	cases
		N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Gender	Females	75 (31.65)	75 (32.61)	19 (25.33)	6 (8.22)	17 (30.91)	27 (30.34)	111 (30.25)	108 (27.55)
	Males	162 (68.35)	155 (67.39)	56 (74.67)	67 (91.78)	38 69.09)	62 (69.66)	256 (69.75)	284 (72.45)
	Total	237 (50.75)	230 (49.25)	75 (50.68)	73 (49.32)	55 (38.19)	89 (61.81)	367 (48.35)	392 (51.65)
Asbestos exposure	No	54 (22.78)	4 (1.74)	41 (54.67)	10 (13.70)	18 (32.73)	3 (3.37)	113 (30.79)	17 (4.34)
	Yes	183 (77.22)	190 (82.61)	34 (45.33)	63 (86.30)	37 (67.27)	86 (96.67)	254 (69.21)	339 (86.48)
	Non-available		36 (15.65)						36 (9.18)
	Age (mean ± SD)	63.36 ± 11.06	67.61 ± 11.14	58.59 ±15.03	69.64 ±9.64	68.31 ±8.80	68.74 ±8.84	63.11 ±12.01	68.25 ±10.39

Table II. Association between MPM and each confounder.

		OR	95% IC	P
Asbestos exposure Yes vs No		8.87	5.20 – 15.15	<0.001
Sex Female vs Male		0.87	0.63 – 1.21	0.4210
Centre	Torino	1.97	1.34 – 2.09	0.001
Casale Monferrato as reference	Genova	1.18	0.18 – 1.73	0.364
Cluster 1 as reference		1.53	1.02 – 2.30	0.040
Age		1.039	1.03 – 1.05	<.001

Table III. SNP genotypes and asbestos-exposure frequencies in MPM cases and controls.

	SNP	EXP	Genotype (code)	Cases (N)	Controls (N)	OR[§]	(95%CI)
1	rs2236304 (*MMP14*)	0	CC (0)	4	57	1	
		0	CG/GG (1)	13	56	3.34	(1.00 – 11.09)
		1	CC (0)	108	116	16.00	(5.45 – 46.98)
		1	CG/GG (1)	231	138	28.87	(9.95 – 83.78)
2	rs742109	0	GG (0)	9	43	1	
		0	AG/AA (1)	8	70	0.52	(0.18 – 1.48)
		1	GG (0)	120	67	10.25	(4.50 – 23.35)
		1	AG/AA (1)	219	187	6.62	(3.03 – 14.46)
3	rs1508805	0	GG (0)	15	63	1	
		0	AG/AA (1)	2	50	0.19	(0.04 – 0.87)
		1	GG (0)	156	158	5.22	(2.74 – 9.94)
		1	AG/AA (1)	183	96	10.33	(5.35 – 19.93)
4	rs2501618 (*CEP350*)	0	GG (0)	14	76	1	
		0	AG/AA (1)	3	37	0.53	(0.14 – 1.99)
		1	GG (0)	212	202	7.20	(3.78 – 13.73)
		1	AG/AA (1)	126	52	17.41	(8.61 – 35.21)
5	rs4701085	0	AA (0)	13	56	1	
		0	AG/GG (1)	4	57	0.31	(0.09 – 1.03)
		1	AA (0)	132	158	4.64	(2.31 – 9.32)
		1	AG/GG (1)	207	106	10.47	(5.17 – 21.20)
6	rs4290865	0	CC (0)	9	64	1	
		0	AC/CC (1)	7	49	0.86	(0.29 – 2.52)
		1	CC (0)	186	182	7.97	(3.73 – 17.03)
		1	AC/CC (1)	148	71	17.21	(7.81 – 37.91)
7	rs9536579	0	GG (0)	11	60	1	
		0	AG/AA (1)	6	53	0.55	(0.19 – 1.64)
		1	GG (0)	221	130	10.93	(5.30 – 22.54)
		1	AG/AA (1)	118	124	5.80	(2.79 – 12.08)
8	rs3801094 (*ETV1*)	0	GG (0)	5	59	1	
		0	AG/AA (1)	12	54	2.94	(0.95 – 9.14)
		1	GG (0)	130	128	15.58	(5.83 – 41.68)
		1	AG/AA (1)	197	122	25.13	(9.42 – 67.07)
9	rs7841347 (*PVT1*)	0	AA (0)	7	37	1	
		0	AG/GG (1)	10	76	0.66	(0.23 – 1.91)
		1	AA (0)	97	54	11.56	(4.60 – 29.06)
		1	AG/GG (1)	242	200	7.42	(3.10 – 17.75)
10	rs10519201 (SHC4)	0	CC (0)	14	86	1	
		0	AC/AA (1)	3	27	0.62	(0.16 – 2.39)
		1	CC (0)	240	215	8.03	(4.23 – 15.23)
		1	AC/AA (1)	99	39	20.21	(9.76 – 41.87)

	SNP	EXP	Genotype (code)	Cases (N)	Controls (N)	OR§	(95%CI)
11	rs5756444	0	AA (0)	3	47	1	
		0	AG\GG (1)	14	66	3.37	(0.90 – 12.64)
		1	AA (0)	146	81	35.83	(10.44 – 112.96)
		1	AG\GG (1)	193	173	21.34	(6.66 – 71.95)
12	rs7632718 (*SLC74A14*)	0	GG (0)	5	28	1	
		0	GA/AA (1)	12	85	0.68	(0.21 – 2.16)
		1	GG (0)	72	88	4.56	(1.62 – 12.92)
		1	GA/AA (1)	267	166	10.04	(3.67 – 27.64)
13	rs9833191 (*THRB*)	0	TT (0)	7	47	1	
		0	TC/CC (1)	10	66	1.22	(0.42 – 3.55)
		1	TT (0)	146	64	19.79	(8.10 – 48.33)
		1	TC/CC (1)	193	190	9.29	(3.91 – 22.06)
14	rs10815216	0	AA (0)	13	38	1	
		0	AC/CC (1)	4	75	0.17	(0.05 – 0.59)
		1	AA (0)	151	80	6.95	(3.33 – 14.51)
		1	AC/CC (1)	188	174	3.92	(1.19 – 8.05)
15	rs73034881 (*SDK1/FOXK1*)	0	GG (0)	14	72	1	
		0	AG/AA (1)	3	41	0.34	(0.09 – 1.29)
		1	GG (0)	253	154	9.73	(5.11 – 18.51)
		1	AG/AA (1)	86	100	5.16	(2.61 – 10.20)

The risks were estimated for each of the 15 SNPs and asbestos exposure. For asbestos exposure "1" indicates exposure, whereas"0" indicates non-exposure. Subject non-exposed (0) and homozygous for the major allele were considered as reference group. § OR (odds ratio) adjusted by age, gender, PCA cluster, center.

Table IV. Results for gene-environment interaction analysis for each candidate SNP and asbestos exposure, adjusted for age, gender, PCA cluster, and centre.

	gene	Deviation from additive model		Deviation from multiplicative model	
		RERI (95% CI)	SI (95% CI)	V	P[#]
1	rs2236304 (*MMP14*)	10.53 (-2.30 – 23.36)	1.61 (1.11 – 2.33)	0.54	0.309
2	rs742109	-3.15 (-7.87 – 1.57)	0.64 (0.41 – 0.99)	1.24	0.780
3	rs1508805[$§‡]	5.92 (1.72 – 10.12)	2.74 (1.60 – 4.69)	10.6	<0.001
4	rs2501618 (*CEP350*)[$‡]	10.69 (2.11 – 19.26)	2.87 (1.77 – 4.63)	4.56	0.016
5	rs4701085[$§‡]	6.52 (1.87 – 11.18)	3.21 (1.76 – 5.88)	7.28	<0.001
6	rs4290865[£‡]	9.38 (1.15 – 17.62)	2.37 (1.52 – 3.70)	2.51	0.106
7	rs9536579[‡]	-4.68 (-9.57 – 0.21)	0.51 (0.33 – 0.77)	0.96	0.951
8	rs3801094 (*ETV1*)	7.61 (-2.17 – 17.39)	1.46 (1.01 – 2.11)	0.55	0.333
9	rs7841347 (*PVT1*)	-3.80 (-9.73 – 2.13)	0.63 (0.40 – 0.99)	0.97	0.964
10	rs10519201 (*SHC4*)[$‡]	12.56 (1.78 – 23.46)	2.89 (1.75 – 4.77)	4.06	0.043
11	rs5756444[&‡]	-16.85 (-41.05 – 7.34)	0.54 (0.38 – 0.78)	0.18	0.005
12	rs7632718 (*SLC74A14*)[£]	5.87 (0.38 – 11.17)	2.78 (1.35 – 5.71)	3.24	0.070
13	rs9833191 (THRB)[‡]	-10.73 (-22.41 – 0.96)	0.45 (0.29 – 0.65)	0.42	0.097
14	rs10815216[&]	-2.20 (-5.23 – 0.83)	0.57 (0.35 – 0.92)	3.32	0.048
15	rs73034881 (*SDK1/FOXK1*)	-3.91 (-7.84 – 0.02)	0.51 (0.33 – 0.81)	1.56	0.537

likelihood ratio test (LRT) for multiplicative interaction term. $ RERI >0, SI >1 and V>1 statistically significant. £ RERI >0, SI >1 statistically significant but V index not statistically significant. & V>1 Statistically significant. RERI Relative Excess Risk due to Interaction, SI Synergy Index, V multiplicative index.
§ V index statistically significant after Bonferroni Correction
‡After Bonferroni correction SI index statistically significant. rs1508805 95%CI 1.21 – 613 ; rs2501618 95% CI 1.39 – 5.89 ; rs4701085 95%CI 1.30 – 7.95; rs4290865 95% CI 1.22 – 4.62; rs9536579 95% CI 0.27 – 0.94; rs10519201 95% CI 1.36 – 6.13; rs5756444 95% CI 0.33 – 0.93; rs9833191 95% CI 0.24 – 0.79.

Table V. Interaction test of multiple SNPs and asbestos exposure in MPM risk: best models assessed by GMDR for one- to five- way combinations. The two best models (see text for details) are in bold.

	TBA	Sign Test (p)	CV	OR (95% CI)	χ^2 (p)
EXP	**0,6339**	**10 (0,001)**	**10/10**	**9.71 (4.20 – 22.44)**	**37.32 (<0.001)**
EXP rs7632718	0,6166	10 (0,001)	6/10	3.88 (2.38 – 6.30)	31.22 (<0.001)
EXP rs4701085 rs1508805	0,6269	10 (0,001)	3/10	5.29 (3,18 – 8.80)	43.85 (<0.001)
EXP rs1508805 rs2501618 rs5756444	**0,6445**	**10 (0,001)**	**5/10**	**6.64 (3.60 – 11.30)**	**53.17 (<0.001)**
EXP rs1508805rs2501618 rs5756444rs7632718	0,6264	10 (0,001)	3/10	7.13 (4.25 – 11.97)	60.21 (<0.001)

MPM: malignant pleural mesothelioma GMDR: generalized multifactor dimensionally reduction.