CHAPTER III

RESULTS

1. The agarose gel of genotyping results

The representative agarose gel of genotyping results of CYP1A1(MspI), CYP1A1(Ilu462Val), CYP2E1(PstI), CYP2E1(DraI), MPO(AciI) and MMP-1(AluI) by PCR-RFLP are shown in Figure 3.1-3.6. The genotyping results of GSTM1 and GSTT1 by multiplex PCR using albumin as an internal PCR control is represented in Figure 3.7. The polymorphism of hOGG1(Ser326Cys) and p53(Arg72Pro) identified by di-allele-specific amplification with artificially modified primers (diASA-AMP) are shown in Figure 3.8-3.9. The genotyping result of hOGG1(Ser326Cys) was confirmed by DNA sequencing and of p53 was confirmed by PCR-RFLP, respectively (data not shown).

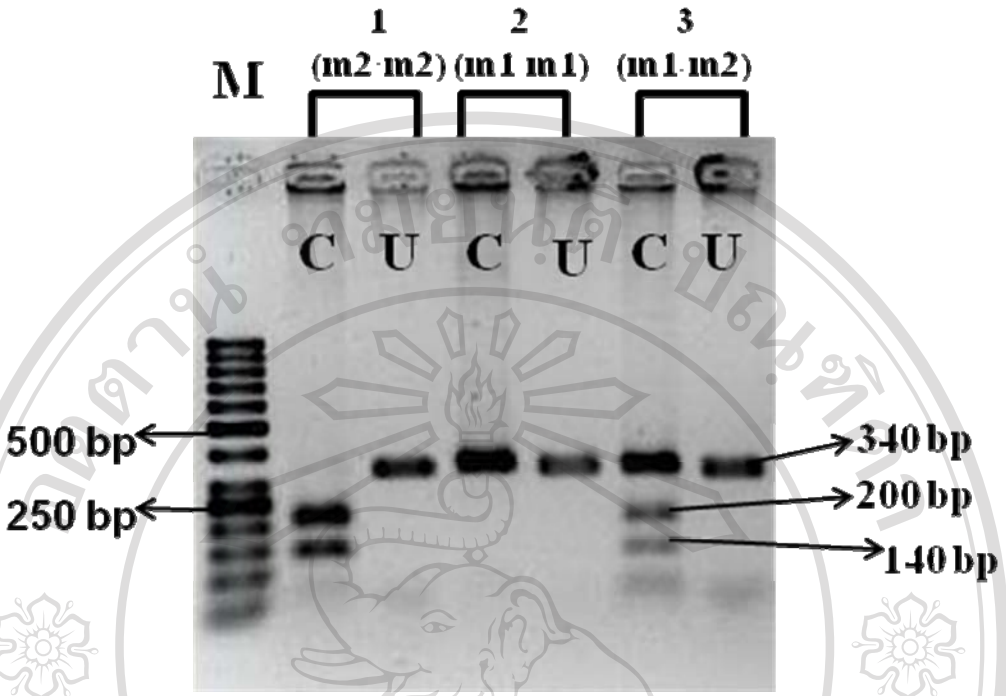

Figure 3.1 Representative examples of agarose gel analysis CYP1A1(MspI) polymorphism. M, DNA molecular size standard. 1=homozygous variant sample (m2/m2), 2= homozygous wild type sample (m1/m1), 3= heterozygous variant sample (m1/m2), C, cut with MspI restriction enzyme and U, uncut

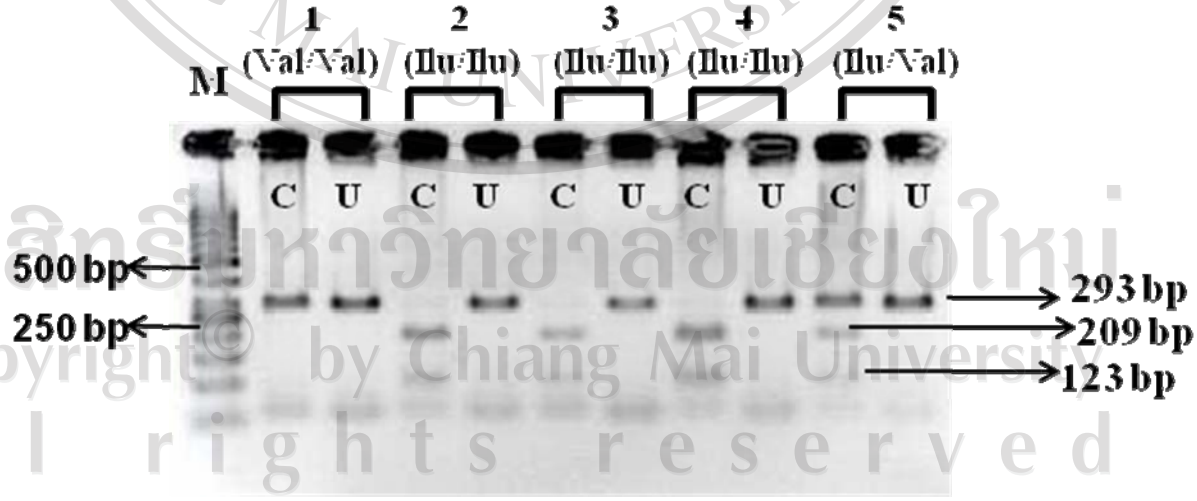

Figure 3.2 Representative agarose gel analysis of CYP1A1 (Ilu462Val) polymorphism. M, DNA molecular size standard. 1=homozygous variant sample (Val/Val), 2, 3 and 4= homozygous wild type samples (Ilu/Ilu), 5=heterozygous variant sample (Ilu/Val), C, cut with BsrDI restriction enzyme and U, uncut

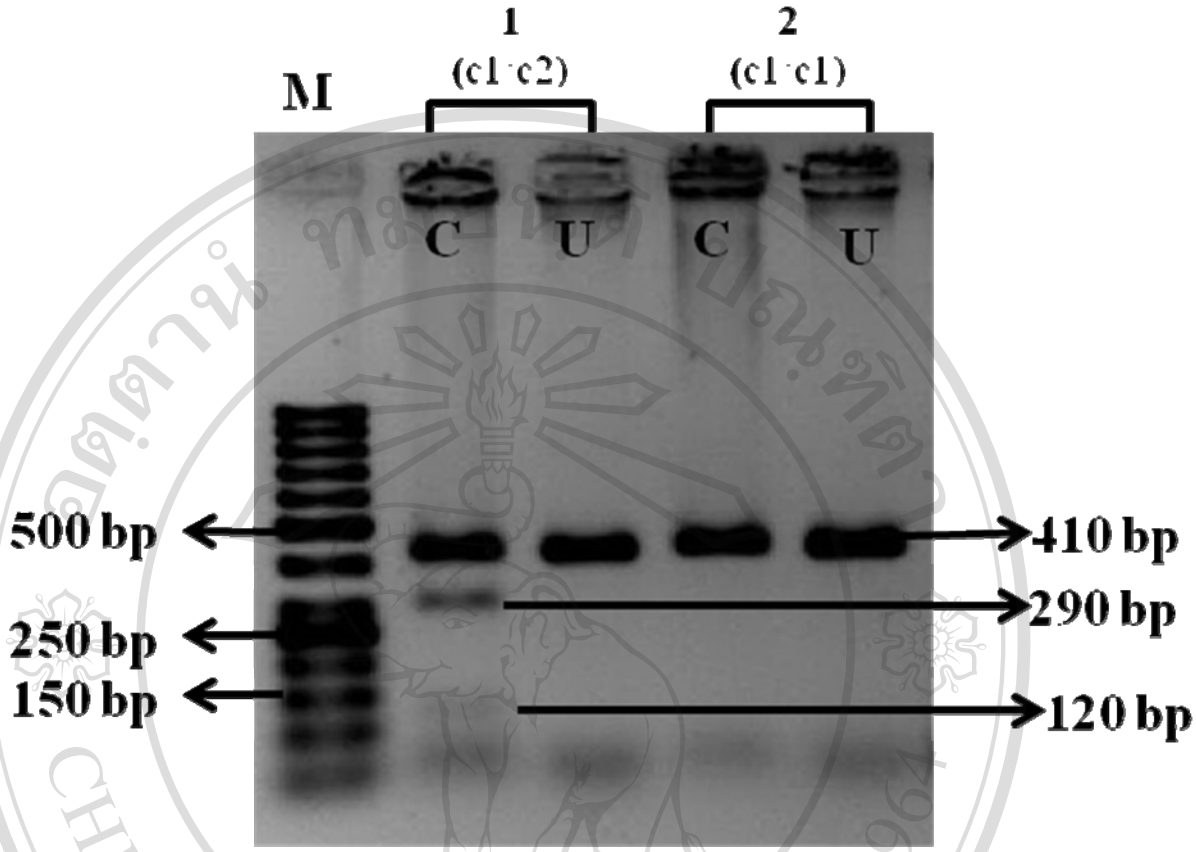

Figure 3.3 Representative agarose gel analysis of CYP2E1 (PstI) polymorphism. M, DNA molecular size standard. 1 = heterozygous variant sample (c1/c2), 2 =homozygous wild type sample (c1/c1), C, cut with PstI restriction enzyme and U, uncut

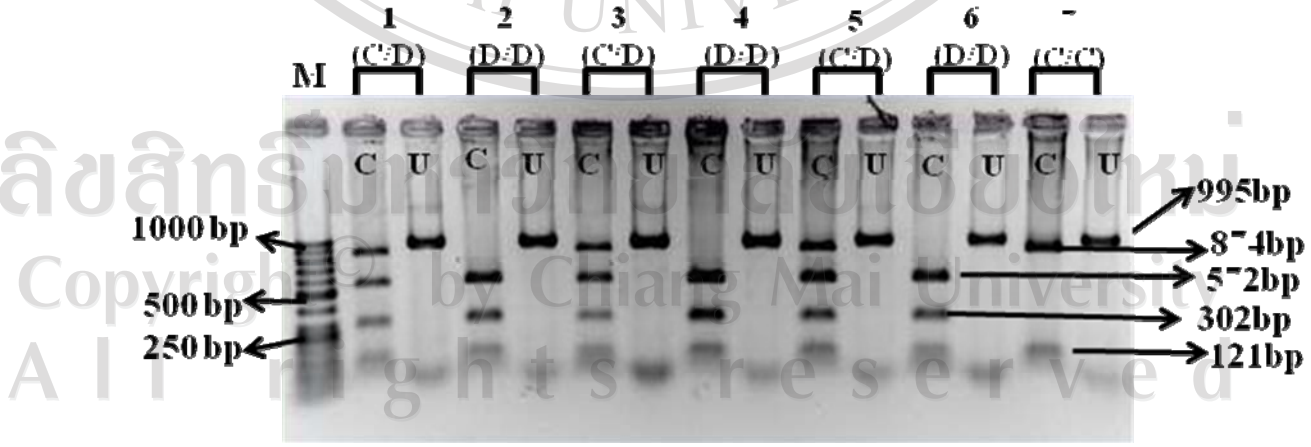

Figure 3.4 Representative agarose gel analysis of CYP2E1 (DraI) polymorphism. M, DNA molecular size standard. 1, 3, 5= heterozygous variant samples (C/D), 2, 4, 6 =homozygous wild type samples (D/D), 7=homozygous variant sample (C/C), C, cut with DraI restriction enzyme and U, uncut

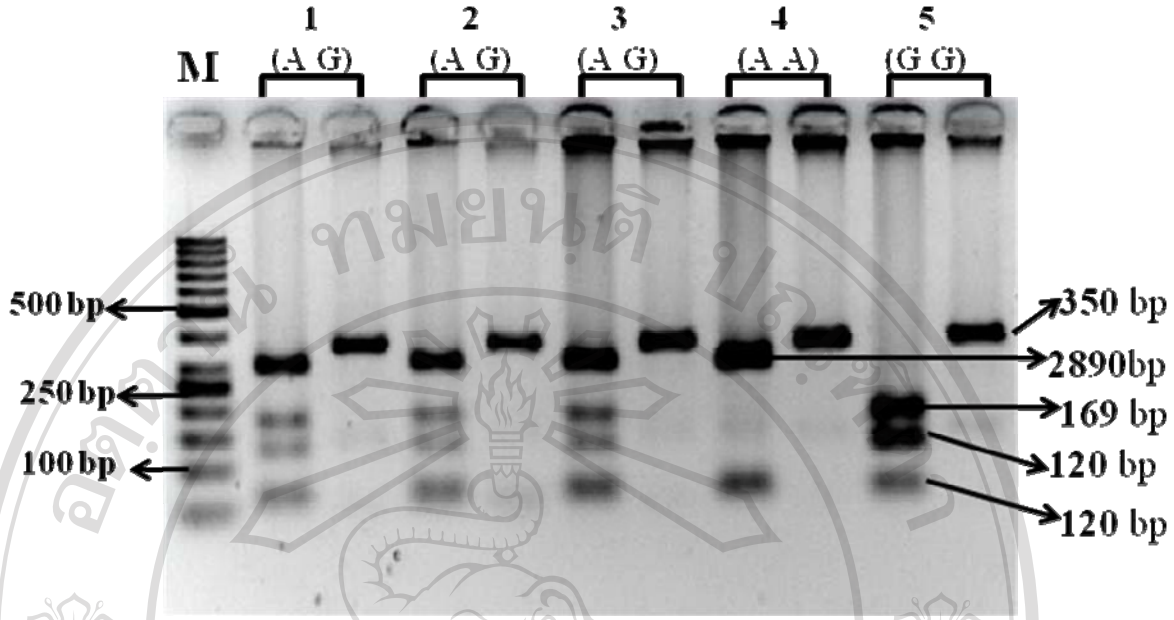

Figure 3.5 Representative agarose gel analysis of MPO (AciI) polymorphism. M, DNA molecular size standard, 1, 2, 3, = heterozygous variant sample (A/G), 4=homozygous variant sample (A/A), 5= homozygous wild type sample (G/G), C, cut with AciI restriction enzyme and U, uncut

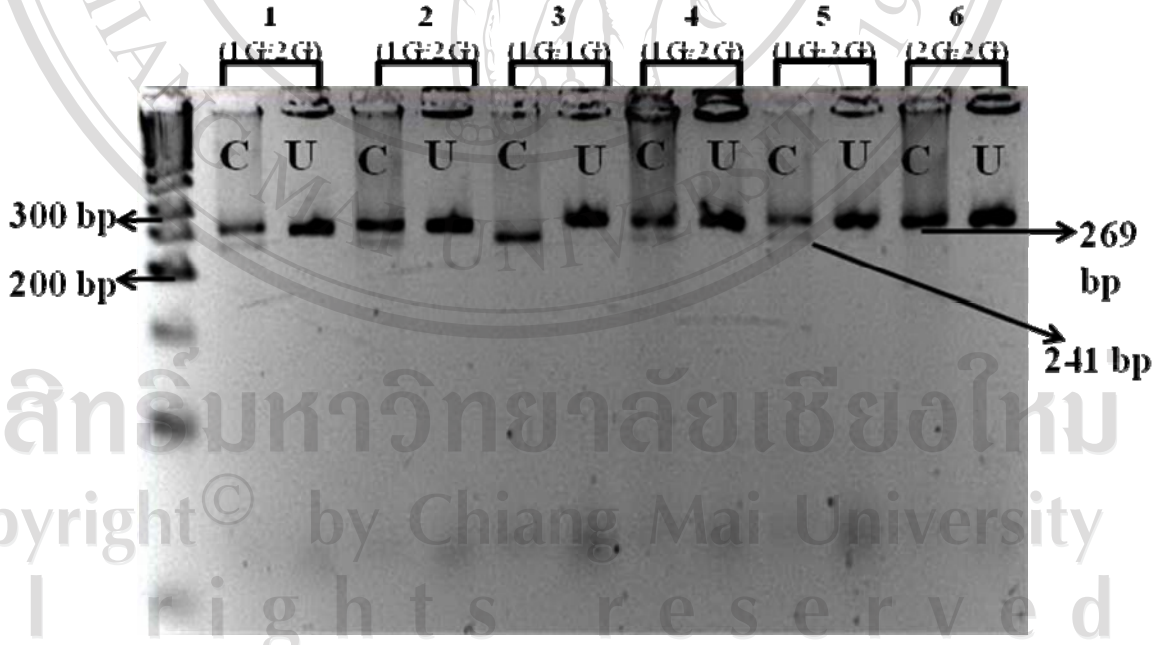

Figure 3.6 Representative agarose gel analysis of MMP-1(AluI) polymorphism. M, DNA molecular size standard. 1, 2, 4, 5= heterozygous variant samples (1G/2G), 3= homozygous wild type sample (1G/1G), 6=homozygous variant sample (2G/2G), C, cut with AluI restriction enzyme and U, uncut

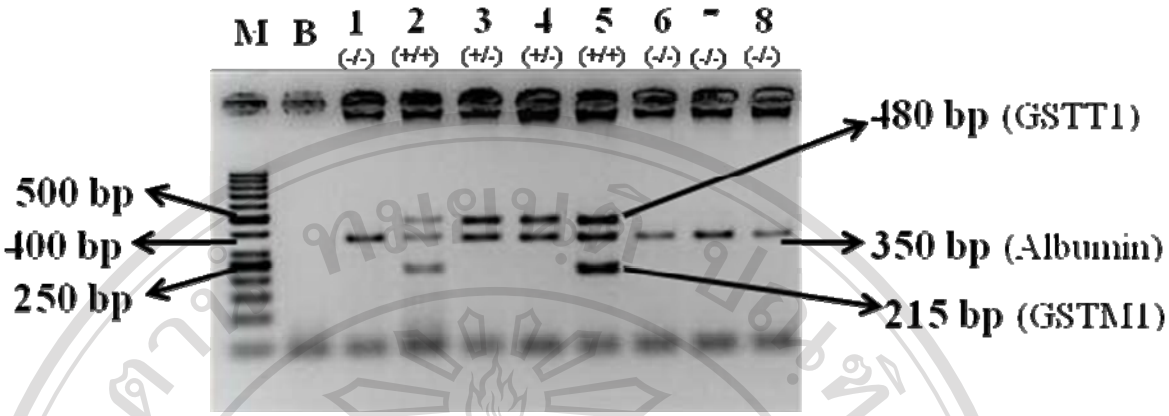

Figure 3.7 Representative of multiplex PCR analysis of GSTT1 and GSTM1 polymorphism, M, DNA molecular size standard, B=blank, lanes 1-8, representative of individual samples. Sample 1, 6, 7 and 8 were classified as GSTT1null/GSTM1null, samples 2, 5 were classified as GSTT1 positive/GSTM1 positive, samples 3, 4 were classified as GSTT1 positive/GSTM1 null samples.

Figure 3.8 Representative agarose gel analysis of hOGG1 (Ser326Cys) polymorphism identified by di-allele-specific amplification with artificially modified primers (diASA-AMP), M, DNA molecular size standard, 1=homozygous wild type sample (Ser/Ser), 2, 3=heterozygous variant samples (Ser/Cys), 4=homozygous variant sample (Cys/Cys)

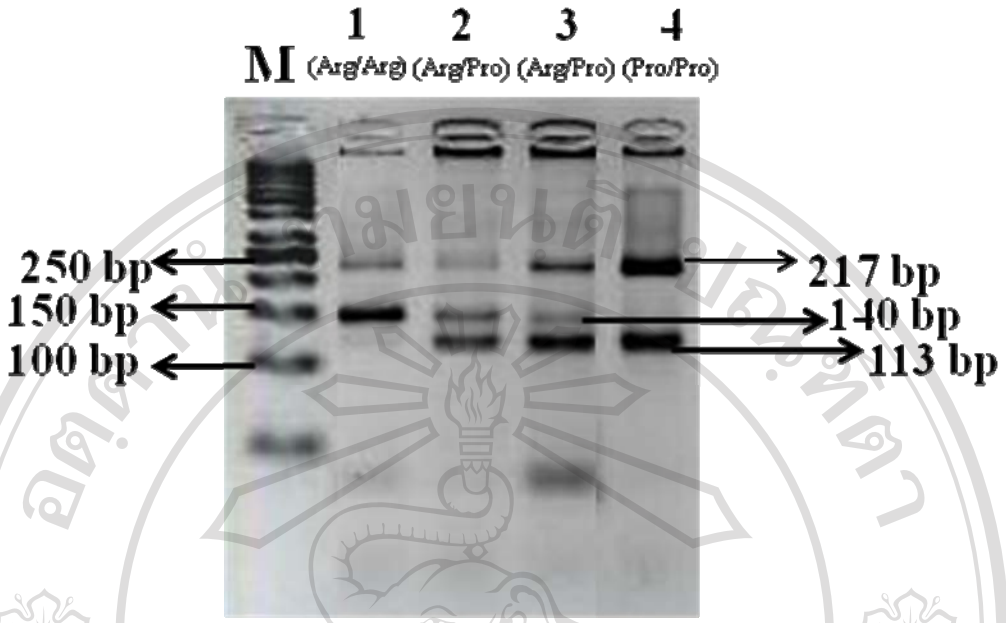

Figure 3.9 Representative agarose gel analysis of p53 (Arg72Pro) polymorphism identified by di-allele-specific amplification with artificially modified primers (diASA-AMP), M, DNA molecular size standard, 1=homozygous wild type sample (Arg/Arg), 2, 3=heterozygous variant samples (Arg/Pro), 4=homozygous variant sample (Pro/Pro)

2. Polymorphic distribution among lung cancer patients and control subjects

The overall polymorphic distribution of CYP1A1(MspI), CYP1A1(Ilu462Val), CYP2E1(PstI), CYP2E1(DraI), GSTM1, GSTT1, MPO(AciI), hOGG1(Ser326Cys), p53(Arg72Pro) and MMP-1(AluI) in cases and controls are summarized in Table 3.1. No significant association (chi-square test) of genetic distributions in relation to lung cancer development was observed in all the investigated genes.

Table 3.1 Distribution of genetic polymorphism between lung cancer cases and controls

Genotypes	Cases (n)	Genotype frequency	Controls (n)	Genotype frequency	P^a
1. CYP1A1 (MspI) (n=167) -Wild type (m1/m1) -Heterozygote (m1/m2) -Homozygous variant (m2/m2)	 85 19 45 21	 0.22 0.53 0.25	 82 16 41 25	 0.20 0.50 0.30	0.692
2. CYP1A1 (Ile462Val) (n=160) -Wild type (Ile/Ile) -Heterozygote (Ile/Val) -Homozygous variant (Val/Val)	 80 33 36 11	 0.41 0.45 0.14	 80 38 33 9	 0.48 0.41 0.11	0.711
3. CYP2E1(PstI) (n=164) -Wild type (c1/c1) -Heterozygote (c1/c2) -Homozygous variant (c2/c2)	83 65 18 0	 0.78 0.22 0	81 60 21 0	 0.74 0.26 0.00	0.527
4. CYP2E1(DraI) (n=163) -Wild type (D/D) -Heterozygote (C/D	82 49 28	 0.60 0.34	81 49 24	 0.60 0.30	0.608

Genotypes	Cases (n)	Genotype frequency	Controls (n)	Genotype frequency	*P*[a]
-Homozygous variant (C/C)	5	0.06	8	0.10	
5. GSTM1 (n= 168) -Positive -Null	87 26 61	 0.30 0.70	81 34 47	 0.42 0.58	0.102
6. GSTT1 (n= 168) -Positive -Null	87 34 53	 0.61 0.39	81 42 39	 0.52 0.48	0.236
7. MPO (AciI) (n= 169) -Wild type (G/G) -Heterozygote (A/G -Homozygous variant (A/A)	88 59 24 5	 0.67 0.27 0.06	81 57 18 6	 0.70 0.22 0.08	0.707
8. hOGG1 (Ser326Cys) (n=151) -Wild type (Ser/Ser) -Heterozygote (Ser/Cys) -Homozygous variant (Cys/Cys)	76 7 31 38	 0.09 0.41 0.50	75 15 34 26	 0.20 0.45 0.35	0.071
9. p53 (Arg72Pro) (n= 157) -Wild type (A/A) -Heterozygote (A/P) -Homozygous variant (P/P)	78 7 37 34	 0.09 0.47 0.44	79 12 39 28	 0.15 0.50 0.35	0.379
10. MMP-1 (AluI) (n= 166) -Wild type (1G/1G) -Heterozygote (1G/2G) -Homozygous variant (2G/2G)	84 9 9 66	 0.11 0.11 0.78	82 14 13 55	 0.17 0.16 0.67	0.248

Table 3.1 (continued.), [a] chi-square test

3. Genetic polymorphism and lung cancer risk

By combining heterozygous and homozygous variants together and using homozygous wild-type as a reference group, ORs of lung cancer risk in relation to the genetic polymorphism of CYP1A1(MspI), CYP1A1(Ilu462Val), CYP2E1(PstI), CYP2E1(DraI), GSM1, GSTT1, MPO(AciI), hOGG1(Ser326Cys), p53(Arg72Pro) and MMP-1(AluI) was calculated. As shown in Table 3.2, no significant change (from 1.0) of ORs was observed in all the genotype investigated. Although, the null genotype of GSTM1 and heterozygous and homozygous variants of hOGG1(Ser326Cys), p53(Arg72Pro) and MMP-1(AluI) showed an increase ORs in comparison to homozygous wild-type reference controls, there were not statistically significant ($p>0.05$). The significance was not seen even after adjusted for age, gender and smoking status (Table 3.2).

The ORs of lung cancer risk in relation to the genetic polymorphism was further calculated with stratification according to gender (Table 3.3). The results showed that heterozygous and homozygous variants of hOGG1(Ser326Cys) significantly increased the risk of lung cancer development among females [OR=8.59 (95% CI:1.04-71.10, p=0.024)].

Table 3.2 Distribution of genetic polymorphism and lung cancer risk

Genotypes	Cases (n)	Controls (n)	OR 95%CI	*p*	OR[a] 95%CI	*p*
1. CYP1A1 (MspI) (n= 167)	75	82		0.652		0.911
-Wild type (m1/m1)	19	16	1.00		1.00	
-Hetero (m1/m2)and Homo variant (m2/m2)	66	66	0.84 (0.40-1.78)		0.95 (0.40-2.25)	
2. CYP1A1 (Ile462Val) (n= 160)	80	80		0.426		0.570
-Wild type (Ile/Ile)	33	38	1.00		1.00	
-Hetero (Ile/Val)and Homo variant (Val/Val)	47	42	1.29 (0.69-2.41)		1.23 (0.60-2.55)	
3. CYP2E1 (PstI) (n= 164)	83	81		0.524		0.865
-Wild type (c1/c1)	65	60	1.00		1.00	
-Hetero (c1/c2) and Homo variant (c2/c2)	18	21	0.79 (0.39-1.63)		0.93 (0.41-2.14)	
4. CYP2E1 (DraI) (n= 163)	82	81		0.923		0.910
-Wild type (D/D)	49	49	1.00		1.00	
-Hetero (C/D) and Homo variant (C/C)	33	32	1.03 (0.55-1.93)		1.04 (0.51-2.13)	
5. GSTM1 (n= 168)	87	81		0.102		0.099
-Positive	26	34	1.00		1.00	
-Null	61	47	1.70 (0.90-3.21)		1.87 (0.89-3.9)	
6. GSTT1 (n= 168)	87	81		0.236		0.298
-Positive	53	42	1.00		1.00	
-Null	34	39	0.69 (0.37-1.28)		0.69 (0.34-1.39)	

Genotypes	Cases (n)	Controls (n)	OR 95%CI	*p*	OR[a] 95%CI	*p*
7. MPO (AciI) (n= 169)	88	81		0.642		0.330
-Wild type (G/G)	59	57	1.00		1.00	
-Hetero (A/G) and Homo variant (A/A)	29	24	1.17 (0.61-2.24)		1.45 (0.68-3.12)	
8. hOGG1 (Ser326Cys) (n=151)	76	75		0.060		0.329
-Wild type (Ser/Ser)	7	15	1.00		1.00	
-Hetero (Ser/Cys) and Homo variant (Cys/Cys)	69	60	2.46 (0.94-6.45)		1.72 (0.58-5.09)	
9. p53 (Arg72Pro) (n= 157)	78	79		0.233		0.181
-Wild type (A/A)	7	12	1.00		1.00	
-Hetero (A/P) and Homo variant (P/P)	71	67	1.82 (0.68-4.90)		2.13 (0.70-6.45)	
10. MMP-1 (AluI) (n= 166)	84	82		0.236		0.165
-Wild type (1G/1G)	9	14	1.00		1.00	
-Hetero (1G/2G) and Homo variant (2G/2G)	75	68	1.72 (0.70-4.22)		2.05 (0.74-5.66)	

Table 3.2 (continued), [a]Adjusted ORs by age, gender and smoking status

Table 3.3 Interaction of genetic polymorphism and gender on lung cancer risk

Genotypes	Females			Males		
	Cases/ controls	**OR (95%CI)**	***p***	**Cases/ controls**	**OR (95%CI)**	***p***
1. CYP1A1 (MspI) -Wild type (m1/m1) -Hetero (m1/m2) and Homo variant (m2/m2)	29/44 4/8 25/36	1.00 1.39 (0.38-5.12)	0.438	56/38 15/8 41/30	1.00 0.73 (0.27-1.90)	0.526
2. CYP1A1 (Ile462Val) -Wild type (Ile/Ile) -Hetero (Ile/Val) and Homo variant (Val/Val)	28/44 12/18 16/26	1.00 0.92 (0.35-2.41)	0.870	52/36 21/20 31/16	1.00 1.85 (0.78-4.36)	0.161
3. CYP2E1 (PstI) -Wild type (c1/c1) -Hetero(c1/c2) and Homo variant (c2/c2)	29/44 26/33 3/11	1.00 0.35 (0.87-1.37)	0.120	54/37 39/27 15/10	1.00 1.04 (0.41-2.66)	0.937
4. CYP2E1 (DraI) -Wild type (D/D) -Hetero (C/D) and Homo variant (C/C)	28/44 18/26 10/18	1.00 0.80 (0.30-2.14)	0.659	54/37 31/23 23/14	1.00 1.219 (0.52-2.86)	0.650
5. GSTM1 -Positive -Null	29/44 10/22 19/22	1.00 1.90 (0.72-5.00)	0.191	58/37 42/25 16/12	1.00 1.26 (0.51-3.09)	0.613
6. GSTT1 -Positive -Null	29/44 19/23 10/21	1.00 0.58 (0.22-1.52)	0.263	58/37 24/18 34/19	1.00 0.75 (0.33-1.71)	0.487
7. MPO (AciI) -Wild type (G/G) -Hetero (A/G) and Homo variant (A/A)	31/44 17/33 14/11	1.00 2.47 (0.93-6.61)	0.068	57/37 42/24 15/13	1.00 0.66 (0.27-1.62)	0.361
8. hOGG1 (Ser326Cys) -Wild type(Ser/Ser) -Hetero(Ser/Cys) and Homo variant (Cys/Cys)	26/43 1/11 25/32	**1.00 8.59 (1.04-71.10)**	**0.019**	50/32 6/4 44/28	1.00 1.05 (0.27-4.05)	0.602
9. p53 (Arg72Pro) -Wild type (A/A) -Hetero(A/P) and Homo variant (P/P)	27/43 1/7 26/36	1.00 5.06 (0.54-43.63)	0.108	51/36 6/5 45/31	1.00 1.21 (0.34-4.32)	0.508

Genotypes	Females			Males		
	Cases/ controls	**OR (95%CI)**	***p***	**Cases/ controls**	**OR (95%CI)**	***p***
10. MMP-1 (AluI) -Wild type (1G/1G) -Hetero(1G/2G) and Homo variant (2G/2G)	30/44 4/8 26/36	1.00 1.44 (0.39-5.31)	0.413	54/38 5/6 49/32	1.00 1.84 (0.52-6.53)	0.264

Table 3.3 (continued.)

3. Multi-loci polymorphisms and lung cancer risk

The effect of genetic polymorphism on lung cancer risk was further investigated by combining different polymorphic variations together. According to the ORs shown in Table 3.2, the effect of genetic variation on the risk of developing lung cancer could be classified into three groups 1) Genes with polymorphisms that did not show any effect on lung cancer risk, ORs (both crude and adjusted ORs) range between 0.8-1.3, which includes CYP1A1(MspI), CYP1A1(Ilu462Val), CYP2E1(DraI) 2) Genes polymorphisms that showed tendency to increase the risk, ORs (either crude or adjusted) > 1.3, which includes GSTM1, MPO(AciI), hOGG1(Ser326Cys), p53(Arg72Pro), MMP-1(AluI) and 3) Genes with polymorphisms that showed tendency to decrease the risk, ORs (either crude or adjusted) < 0.8, which includes GSTT1 and CYP2E1(PstI). ORs of different combinations of genes within group 2 and 3 were calculated to further investigate whether there is an enhanced effect of any two polymorphic combinations on increasing or reducing the risk of lung cancer. The ORs of eleven genetic-variant combinations are shown in Table 3.4. Although, each individual isolated genetic variant did not show any significant effect on the overall ORs (Table 3.2), a number of variant genotype combination showed a significant effect on increasing the risk of lung cancer risk. The combinations that showed a significant increase ($p<0.05$) of ORs in comparison to wild-type genotype are the variants combination of GSTM + p53(Arg72Pro) (adjusted OR = 2.37), GSTM + MMP-1(AluI) (crude OR = 1.90), hOGG1(Ser326Cys) + p53(Arg72Pro) (crude OR = 2.61), hOGG1(Ser326Cys) + MMP-1(AluI) (crude OR = 2.08) and hoGG1(Ser326Cys) + MPO(AciI) (crude OR = 3.72 and adjusted OR = 6.88). Both crude OR and adjusted OR of variants

combination of CYP2E1(PstI) + GSTT1 in comparison to homozygous wild-type genotype was decreased to 0.47 and 0.54 respectively, however, it was not statistically significant.

Table 3.4 Effect of combined genetic polymorphisms on lung cancer risk

Genotypes	**Cases (n)**	**Controls (n)**	**OR 95%CI**	***p***	**OR[a] 95%CI**	***p***
1. GSTM1+p53	78	78		0.053		**0.025**
- null and Pro/Pro or Arg/Pro	49	37	1.87		**2.37**	
- the rest	29	41	(0.99-3.55)		**(1.11-5.05)**	
			1.00		**1.00**	
2. GSTM1+MPO	74	78		0.707		0.659
- null and G/G or A/G	20	19	1.15		1.21	
- the rest	54	59	(0.56-2.38)		(0.52-2.79)	
			1.00		1.00	
3. GSTM-1+hOGG1	77	75		0.259		0.265
- null and Cys/Cys or Ser/Cys	44	36	1.44		1.53	
- the rest	33	39	(0.76-2.74)		(0.72-3.26)	
			1.00		1.00	
4.GSTM1+MMP-1	83	81		**0.043**		0.060
- null and 2G/2G or 1G/2G	51	37	**1.90**		1.99	
- the rest	32	44	**(1.02-3.53)**		(0.97-4.11)	
			1.00		1.00	
5. hOGG1+ p53	76	73		**0.015**		0.062
- both variants	64	49	**2.61**		2.33	
- the rest	12	24	**(1.19-5.74)**		(0.96-5.67)	
			1.00		1.00	
6. hOGG1+MPO	75	75		**0.020**		**0.006**
- both variants	13	4	**3.72**		**6.88**	
- the rest	62	71	**(1.15-12.01)**		**(1.76-26.79)**	
			1.00		**1.00**	
7.hOGG1+MMP-1	76	75		**0.033**		0.068
- both variants	34	21	**2.08**		2.09	
- the rest	42	54	**(1.06-4.10)**		(0.95-4.63)	
			1.00		1.00	
8. p53+MPO	78	78		0.585		0.198
- both variants	22	19	1.22		1.74	
- the rest	56	59	(0.60-2.50)		(0.75-4.07)	
			1.00		1.00	

Genotypes	Cases (n)	Controls (n)	OR 95%CI	*p*	OR[a] 95%CI	*p*
9. p53+MMP-1	77	78		0.148		0.158
- both variants	62	55	1.72		1.85	
- the rest	15	23	(0.82-3.64)		(0.79-4.32)	
			1.00		1.00	
10. MPO+MMP-1	83	81		0.550		0.339
- both variants	25	21	1.23		1.47	
- the rest	58	60	(0.62-2.44)		(0.67-3.26)	
			1.00		1.00	
11. CYP2E1(PstI) + GSTT1				0.175		0.330
	80	80	0.47		0.54	
- both variants	5	10	(0.15-1.43)		(0.15-1.88)	
- the rest	75	70	1.00		1.00	

Table 3.4 (continued.), [a] ORs adjusted for age, gender and smoking status
Both variants = carrying at least one variant allele (heterozygous or homozygous) and GSTM1 null on both genes; the rest = one or both of the genes is homozygous wild-type

ORs of each variant combination were further investigated with stratification to gender. As shown in Table 3.5, while no significant effect was seen in males, variant genotype of hOGG1(Ser326Cys) in combination with variant genotype of p53(Arg72Pro) or MPO(AciI) remarkably increase OR to 15.39 (95%CI: 1.90-124.83, p = 0.02) and 9.11 (95%CI: 1.76-47.23, p = 0.05) among females, respectively. The risk of lung cancer was further investigated with stratification to gender as well as smoking status; the result is shown in Table 3.6. Interestingly, the risk increasing effects of GSTM null genotype when combined with variant genotype of p53(Arg72Pro) or hOGG1(Ser326Cys) or MMP-1(AluI) were significantly ($p<0.05$) potent in female-nonsmokers with the ORs of 6.60 (95%CI: 1.25-34.95), 6.86 (95%CI: 1.27-36.93) and 3.86 (95%CI: 1.00-14.87), respectively.

Effect of multi-loci combination of GSTM1, MPO(AciI), hOGG1(Ser326Cys), p53(Arg72Pro), MMP-1(AluI) on lung cancer risk was further investigated and the result is shown in Table 3.7. By using a group of individual who carrying 2 or more wild-type genotype of these 5 genes (positive genotype for GSTM1, homozygous wild-type for all the other genes), it was found that an individual who carrying 3 or more variant genotype of these 5 genes is at significantly higher risk of developing lung cancer with the OR of 3.322 (95%CI: 1.13-9.77). When a group of 3 or more variants carrying was subdivided into 3 different groups, including a group of individual who carrying 3, 4 and 5 variants, the result shows that OR was raised in concurrence with the increased number of variant genes. The ORs was 2.41 (95%CI: 0.76-7.64, p=0.128), 3.90 (95%CI: 1.23-12.34, p=0.017) and 5.20 (95%CI: 1.31-20.54, p=0.015) for individual carrying 3, 4 and 5 variants, respectively. Fascinatingly, when the OR was calculated with stratification of gender, the same, but more powerful, pattern was observed with the ORs of 4.05 (95%CI: 0.44-36.94, p=0.189), 9.00 (95%CI: 0.95-84.89, p=0.037) and 18.00 (95%CI: 1.49-216.62, p=0.017) for female individual who carrying 3, 4 and 5 variants of these 5 genes, respectively (Table 3.7).

Table 3.5 Interaction between combined genetic polymorphisms and gender on lung cancer risk

Genotypes	Females			Males		
	Cases/ controls	**OR (95%CI)**	***p***	**Cases/ controls**	**OR (95%CI)**	***p***
1. GSTM1+p53			0.156			0.332
- null and Pro/Pro or Arg/Pro	27/43	2.02		51/35	1.54	
- the rest	16/18	(0.76-5.37)		33/19	(0.64-3.71)	
	11/25	1.00		18/16	1.00	
2. GSTM1+MPO			0.287			0.692
- null and G/G or A/G	24/42	1.83		50/36	0.82	
- the rest	8/9	(0.60-5.64)		12/10	(0.31-2.18)	
	16/33	1.00		38/26	1.00	
3. GSTM-1+hOGG1			0.097			0.611
- null and Cys/Cys or Ser/Cys	26/43	2.30		51/32	0.79	
- the rest	15/16	(0.85-6.22)		29/20	(0.32-1.96)	
	11/27	1.00		22/12	1.00	
4.GSTM1+MMP-1	29/44		0.113	54/37		0.438
- both variants	16/16	2.15		35/21	1.40	
- the rest	13/28	(0.83-5.60)		19/16	(0.60-3.31)	
		1.00			1.00	
5. hOGG1+ p53	26/42		**0.020**	50/31		0.694
- both variants	25/26	**15.39**		39/23	1.23	
- the rest	1/16	**(1.90-124.83)**		11/8	(.43-3.51)	
		1.00			1.00	
6. hOGG1+MPO	26/43		**0.005**	49/32		0.698
- both variants	8/2	**9.11**		5/2	1.71	
- the rest	18/41	**(1.76-47.23)**		44/30	(0.31-9.37)	
		1.00			1.00	
7.hOGG1+MMP-1	26/43	2.31	0.101	50/32	2.17	0.116
- both variants	13/13	(0.84-6.32)		21/8	(0.82-5.77)	
- the rest	13/30	1.00		29/24	1.00	
9. p53+MMP-1	27/43	2.12	0.199	50/35	1.39	0.534
- both variants	22/29	(0.67-6.77)		40/26	(0.50-3.87)	
- the rest	5/14	1.00		10/9	1.00	
10.MMP-1+ MPO	29/44	2.75	0.053	54/37	0.661	0.380
- both variants	12/9	(0.97-7.77)		13/12	(0.26-1.67)	
- the rest	17/35	1.00		41/25	1.00	

Genotypes	Females			Males		
	Cases/ controls	**OR (95%CI)**	***p***	**Cases/ controls**	**OR (95%CI)**	***p***
11. CYP2E1(PstI) + GSTT1 - both variants - the rest	28/44 1/6 27/38	0.24 (0.027-2.06) 1.00	0.235	52/36 4/4 48/32	0.67 (0.156-2.86) 1.00	0.711

Table 3.5 (continued.) Both variants = carrying at least one variant allele (heterozygous or homozygous) GSTM1 null on both genes; the rest = one or both of the genes is homozygous wild-type

Table 3.6 Interaction between combined genetic polymorphisms and gender and smoking status on lung cancer risk

Genotypes	Females						Males					
	Non-smokers			Smokers			Non-smokers			Smokers		
	Cases/ controls	OR (95%CI)	*p*	Cases/ controls	OR (95%CI)	*p*	Cases/ controls	OR (95%CI)	*p*	Cases/ controls	OR (95%CI)	*p*
1. GSTM1+p53 - null and Pro/Pro or Arg/Pro - the rest	11/37 9/15 2/22	**6.60 (1.25-34.95)** **1.00**	**0.016**	16/6 7/3 9/3	0.78 (0.12-5.10) 1.00	1.000	4/15 3/10 1/5	1.50 (0.12-18.36) 1.00	1.000	47/20 30/9 17/11	2.16 (0.75-6.25) 1.00	0.153
2. GSTM1+MPO - null and G/G or A/G - the rest	11/37 4/8 7/29	2.07 (0.48-8.89) 1.00	0.430	13/5 4/1 9/4	1.78 (0.15-21.40) 1.00	1.000	4/15 1/3 3/12	1.33 (0.10-17.82) 1.00	1.000	46/21 11/7 35/14	0.63 (0.20-1.95) 1.00	0.420
3. GSTM-1+hOGG1 - null and Cys/Cys or Ser/Cys - the rest	10/38 8/14 2/24	**6.86 (1.27-36.93)** **1.00**	**0.029**	16/5 7/2 9/3	1.17 (0.15-9.01 1.00)	1.000	4/13 2/9 2/4	0.44 (0.045-4.37) 1.00	0.584	47/19 27/11 20/8	0.98 (0.33-2.87) 1.00	0.973
4.GSTM1+MMP-1 - both variants - the rest	13/38 9/14 4/24	**3.86 (1.00-14.87)** **1.00**	**0.043**	16/6 7/2 9/4	1.56 (0.22-11.09) 1.00	1.000	4/16 3/9 1/7	2.33 (0.20-27.57) 1.00	0.619	50/21 32/12 18/9	1.33 (0.47-3.77) 1.00	0.587
5. hOGG1+ p53 - both variants - the rest	10/37 10/22 0/15	**1.68 (1.29-2.19)** **1.00**	**0.019**	16/5 15/4 1/1	1.17 (0.74-1.85 1.00	0.429	4/12 2/10 2/2	0.60 (0.22-1.65) 1.00	0.245	46/19 37/13 9/6	1.18 (0.84-1.65) 1.00	0.340
6. hOGG1+MPO - both variants - the rest	10/38 3/2 7/36	7.71 (1.08-54.98) 1.00	0.054	16/5 5/0 11/5	0.69 (0.50-0.96) 1.00	0.278	4/13 2/1 2/12	12.00 (0.71-203) 1.00	0.121	45/19 3/1 42/18	1.29 (0.13-13.21) 1.00	1.000

Genotypes	Females						Males					
	Non-smokers			Smokers			Non-smokers			Smokers		
	Cases/ controls	OR (95%CI)	*p*	Cases/ controls	OR (95%CI)	*p*	Cases/ controls	OR (95%CI)	*p*	Cases/ controls	OR (95%CI)	*p*
7.hOGG1+MMP-1 - both variants - the rest	10/38 4/12 6/26	1.44 (0.34-6.09) 1.00	0.712	16/5 9/1 7/4	5.14 (0.47-56.90) 1.00	0.311	4/13 2/3 2/10	3.33 (0.32-34.8) 1.00	0.538	46/19 19/5 27/14	1.97 (0.61-6.40) 1.00	0.255
8. p53+MPO - both variants - the rest	11/37 5/10 6/27	2.25 (0.56-9.04) 1.00	0.283	16/6 6/0 10/6	0.63 (0.43-0.91 1.00)	0.133	4/15 2/4 2/11	2.75 (0.28-26.6) 1.00	0.557	47/20 9/5 38/15	0.71 (0.20-2.47) 1.00	0.744
9. p53+MMP-1 - both variants - the rest	11/37 9/25 2/12	2.16 (0.40-11.57) 1.00	0.305	16/6 13/4 3/2	2.17 (0.26-17.89) 1.00	0.419	3/14 2/12 1/2	0.33 (0.02-5.64) 1.00	0.465	47/21 38/14 9/7	2.11 (0.66-6.75) 1.00	0.167
10.MMP-1+ MPO - both variants - the rest	12/38 5/9 7/29	2.30 (0.59-9.06) 1.00	0.198	17/6 7/0 10/6	4.20 (0.40-43.47) 1.00	0.218	4/16 2/5 2/11	2.20 (0.24-20.3) 1.00	0.439	50/21 11/7 39/14	0.56 (0.18-1.74) 1.00	0.316
11. CYP2E1(PstI) + GSTT1 - both variants - the rest	12/38 0/6 12/32	1.19 (1.04-1.36) 1.00	0.314	16/6 1/0 15/6	0.94 (0.83-1.06) 1.00	1.000	4/15 0/2 4/13	1.15 (0.95-1.41) 1.00	1.000	48/21 4/2 44/19	1.01 (0.86-1.19) 1.00	1.000

Table 3.6 (continued.) Both variants = carrying at least one variant allele (heterozygous or homozygous) and GSTM1 null on both genes; the rest = one or both of the genes is homozygous wild-type

Table 3.7 Effect of muti-loci[a] polymorphisms on lung cancer risk

Genotypes	Both genders			Females			Males		
	n (cases/controls)	**ORs (95% CI)**	***p***	**n (cases/controls)**	**ORs (95% CI)**	***p***	**n (cases/controls)**	**ORs (95% CI)**	***p***
1. Individuals with 2 or more wild-type genes (reference)	19 (5/14)	1.00		10 (1/9)	1.00		9(4/5)	1.00	
2. Individuals with 3 or more variant genes[b]	**129 (70/59)**	**3.32 (1.13-9.77)**	**0.023**	**58 (25/33)**	**6.82 (0.81-57.39)**	**0.045**	71 (45/26)	2.16 (0.53-8.78)	0.229
3. Individuals with 3 variant genes	54 (25/29)	2.41 (0.76-7.64)	0.128	29(9/20)	4.05 (0.44-36.94)	0.189	25(16/9)	2.22 (0.47-36.94)	0.264
4. Individuals with 4 variant genes	**55 (32/23)**	**3.90 (1.23-12.34)**	**0.017**	**20(10/10)**	**9.00 (0.95-84.89)**	**0.037**	35(22/13)	2.12 (0.48-9.31)	0.265
5. Individuals with 5 variant genes	**20 (13/7)**	**5.20 (1.31-20.54)**	**0.015**	**9(6/3)**	**18.00 (1.49-216.62)**	**0.017**	11(7/4)	2.19 (0.36-13.22)	0.342

[a] Genetic polymorphism of GSTM1, MPO(aciI), hOGG1(Ser326Cys), p53(Arg72Pro), MMP-1(AluI)

[b] Variant gene means null genotype for GSTM1, homozygous + heterozygous variant for all the other gen