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Research Paper

The Interaction of Smoking with Gene Polymorphisms on Four Digestive Cancers: A Systematic Review and Meta-Analysis

Le Du[1,2], Lei Lei[1,2], Xiaojuan Zhao[1,2], Hongjuan He[1,2], Erfei Chen[1,2], Jing Dong[1,2], Yuan Zeng[1,2], Jin Yang[1,2]✉

1. Key Laboratory of Resources Biology and Biotechnology in Western China, Ministry of Education, College of Life Science, Northwest University, Xi'an 710069, China
2. Institute of Preventive Genomic Medicine, Xi'an 710069, China

✉ Corresponding author: Jin Yang, email: yangjin@nwu.edu.cn; telephone: 86-13572177146

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Abstract

The main purpose of this study was to perform a meta-analysis to assess the interaction between smoking and nine genes (*GSTM1*, *GSTT1*, *GSTP1*, *CYP1A1*, *NAT2*, *SULT1A1*, *hOGG1*, *XRCC1* and *p53*) on colorectal cancer, gastric cancer, liver cancer and oesophageal cancer. Published articles from the PubMed, ISI and EMBASE databases were retrieved. A total of 67 case–control studies or nested case–control studies were identified for the analysis. The pooled jodds ratio (OR) with 95% confidence interval (CI) was calculated using the random effect model. The overall study showed that the *GSTM1* polymorphism was associated with the risk of the four digestive cancers among Asian population (OR 1.284, 95% CI: 1.122-1.470, *p*: 0). Subgroup analyses by cancer site showed that *GSTM1* null genotype increased the gastric cancer risk in total population (OR 1.335, 95% CI: 1.145-1.556, *p*: 0). However, the association of *GSTM1* null genotype with the oesophageal cancer risk was found in smokers (OR 1.382, 95% CI: 1.009-1.894, *p*:0.044), but not in non-smokers (OR 1.250, 95% CI: 0.826-1.891, *p*:0.290). Moreover, smokers with the *CYP1A1* Ile462Val polymorphism were at an increased cancer risk in Asian population (OR=1.585, 95% CI 1.029-2.442, *p*: 0.037). None of the other gene-smoking interactions was observed in the above cancers. This meta-analysis reveals two potential gene-smoking interactions, one is between smoking and *GSTM1* on oesophageal cancer, and the other is between smoking and *CYP1A1* Ile462Val on the four cancers in Asian population. Future studies need to be conducted to verify the conclusions.

Key words: gene polymorphisms; gene-smoking interaction; digestive cancer; meta-analysis

Introduction

Cancer was the second leading cause of non-communicable diseases deaths worldwide in 2015. Most cancer patients die from digestive cancers between 2005 and 2015, of which the death toll increased to 832,000 for colorectal cancer (CRC), 818.9,000 for gastric cancer (GC), 810.5,000 for liver cancer (LC) and 439,000 for oesophageal cancer (OC)[1]. Moreover, the incidence of these four cancers ranks in the top ten over the world, mainly in developing countries [2]. Especially, these cancers are generally recognized as tobacco-related cancers (TRCs) by the International Association of Research in Cancer (IARC) [3]. However, not all individuals exposed to tobacco develop these cancers. Because the etiology of cancer is multifactorial and complicated [4], cigarette smoking, as a prevalent environment factor, may interact with multiple genetic factors, leading to a higher susceptibility to cancer.

The research on the gene-smoking interaction in cancer risk has been popular [5]. Previously published studies clarified the molecular mechanism of the gene-smoking interaction. Most tobacco carcinogens first form DNA adducts via metabolic activation; persistent DNA adducts induce mutations in some

critical genes and initiate carcinogenesis [6]. The elimination of DNA adducts requires DNA repair, implying that variations of the DNA repair genes may be related to different repair efficiencies of DNA damage [7]. Moreover, various detoxification pathways are competitive and different individuals have distinct balances between metabolic activation and detoxification, influencing the cancer risk [8]. Increasing epidemiologic studies and meta-analyses have indicated the interaction between smoking and gene polymorphisms in various cancer types [9-11]. However, most meta-analyses only assessed the interaction between single gene polymorphism and smoking on one or several cancers. Furthermore, the results were inconsistent or even conflicting. Hence, we performed a comprehensive meta-analysis on the interaction of smoking with ten gene polymorphisms in four digestive cancers. The aim was to develop a more powerful evaluation of gene–smoking interaction on major digestive cancers risk.

Materials and methods

Search strategy

PubMed, ISI and EMBASE databases were searched until Dec. 2017 with combinations of the following keywords: "smoke, cigarette, tobacco, smoking", "gene, polymorphism", "colorectal, colon, rectum, colorectum, liver, hepatocellular, oesophageal, oesophagus, gastric, stomach", and "cancer, carcinoma, adenomas". No restrictions were placed on language. References of the retrieved and review articles were also screened by hand.

Inclusion and exclusion criteria

Studies that were included in our analysis had to meet all of the following criteria: (1) evaluated the gene–smoking interaction on the risk of digestive cancers; (2) only case–control studies or cohort studies were considered; (3) provided case and control or cohort size by gene-smoking interaction; (4) showed the gene polymorphisms that were evaluated in at least five independent studies on the four digestive cancers and (5) when an author had several studies on the same patient population, only the most recent or largest sample article was included..The following exclusion criteria were used: (1) the full text was not obtained; (2) only case population; and (3) duplicated study.

Data extraction and quality assessment

All data were independently extracted by two investigators according to the above selection criteria. The information collected from each study are as follows: the first author's last name; year of publication; country of origin; ethnicity; study design; total number of cases and controls or cohort; cancer type; gene names; number of cases and controls or cohort by gene polymorphisms; number of cases and controls or cohort by gene-smoking interaction. Smoking habits were categorized as non-smoker and smoker. The number of cases and controls or cohort by gene-smoking interaction was extracted according to four combinations: non-smoker + "no risk" polymorphism; non-smoker + "at risk" polymorphism; smoker + "no risk" polymorphism; and smoker + "at risk" polymorphism. For each gene polymorphism, the "at risk" phenotype was identified based on known biological mechanisms and the classification conducted by most included articles. "At risk" polymorphism for *GSTM1/GSTT1* was the null (−/−); for *GSTP1*, the Ile105Val substitution (Ile/Val+Val/Val); for *CYP1A1*, the 3801T>C substitution (MspI) (T/C+C/C) and Ile462Val substitution (Ile/Val+Val/Val), for *NAT2*, the fast + intermediate (at least one *4 or *12) acetylator; for *SULT1A1*, the slow+intermediate (at least one *2) sulphation, for *hOGG1*, the Ser326Cys substitution (Ser/Cys+Cys/Cys); for *XRCC1*, the Arg399Gln substitution (Arg/Gln+Gln/Gln); and for *p53*, the Arg72Pro substitution (Arg/Pro +Pro/Pro).

The quality of each study was evaluated by the Newcastle-Ottawa Scale (NOS), which is a 9-star system containing the following three dimensions: selection; comparability; and outcome (cohort studies) or exposure (case-control studies) [12]. A study with 7-9 scores was classified as a high-quality study, while those with scores of 4–6 and 0-3 are moderate- and low-quality studies, respectively [13].

Statistical methods

The reference group was identified as "no risk" polymorphism, and the odds ratios (OR) with 95% confidence intervals (CI) were calculated to determine a risk of the association between gene polymorphisms and digestive cancers. To be conservative, the random effects model was applied to calculate the summary risk. In addition, the subgroup analyses were conducted based on the cancer site and ethnicity. Heterogeneity was evaluated among studies by calculating the *Q*-statistic and I^2 value [14]. Publication bias was assessed by constructing the funnel plots (there was no publication bias if the funnel plot was symmetric) and quantified using Begg's test and Egger's test [15, 16], in which a p-value<0.05 indicated the presence of potential publication bias. All statistical analyses were performed using Comprehensive Meta-Analysis Software, version v. 2.0 (CMA, Biostat, Englewood, NJ, USA). For the positive findings, the false-positive report probability and statistical power were calculated by G*Power software [17, 18].

Results

Literature search

A total of 1979 articles were collected from the 3 databases. As shown in Figure 1, 1491 publications were excluded; 1251 articles were titles, abstracts, systematic reviews, meta-analyses, case reports and irrelevant articles and another 240 papers lacked data on gene-smoking interactions. Finally, a total of 67 studies were included in this meta-analysis. The reason for removing 421 studies from the remaining articles was that they evaluated the gene polymorphisms in less than five independent studies on the four digestive cancers.

Study characteristics and quality assessment

Study characteristics are summarized in Table 1. These studies were case–control or nested case–control studies, including 21,954 cases and 30,341 controls. Forty-three studies were performed in Asia, 11 studies were performed in Europe, 10 studies were performed in the Americas, and 3 studies were performed in Africa. Among all identified articles, 30 evaluated *GSTM1* polymorphism [19-48], 18 evaluated *GSTT1* polymorphism [20-24, 30-32, 34, 35, 40, 42-48], 12 evaluated *GSTP1* polymorphism [11, 22, 30, 32, 34, 35, 42, 49-53], 8 evaluated *CYP1A1* IIe462Val polymorphism [9, 27, 28, 54-58], 7 evaluated *CYP1A1* MspI polymorphism [26, 28, 45, 54, 57, 58], 8 evaluated *NAT2* polymorphism [24, 28, 36, 38, 46, 59-61], 6 evaluated *SULT1A1* polymorphism [24, 45, 62-65], 8 evaluated *hOGG1* polymorphism [66-73], 7 evaluated *XRCC1* polymorphism [52, 67, 69, 74-77], and 6 evaluated *p53* polymorphism [78-83].

As shown in Table 1, the quality scores of studies ranged from 6 to 9. Therefore, 91% of the studies (n=61) were high-quality studies (studies with a score ≥7).

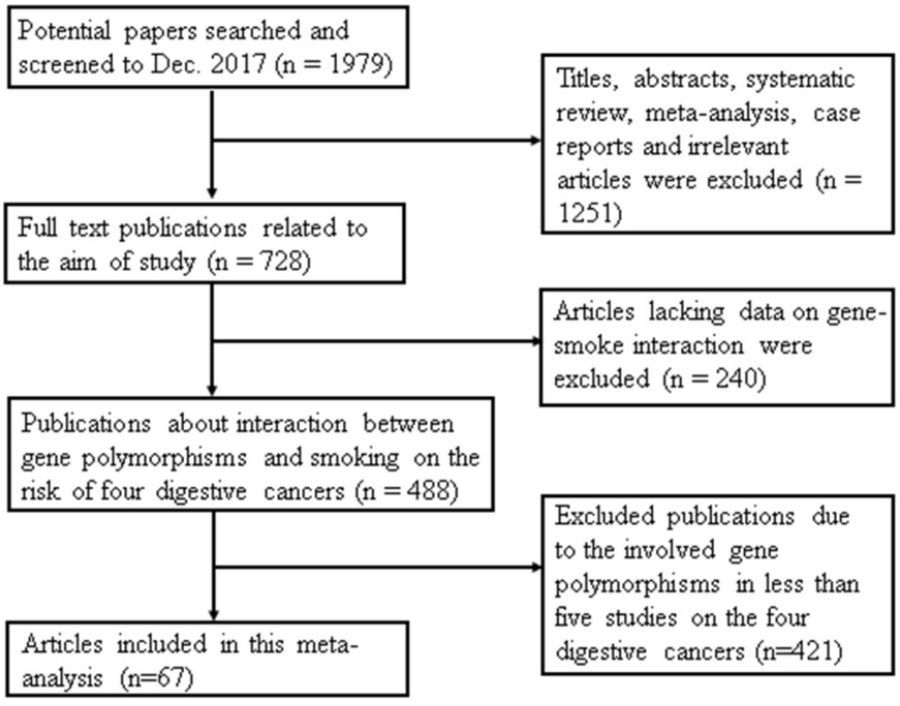

Figure 1. Flow diagram of study selection in this meta-analysis. This flowchart indicates that the process of screening relevant studies based on the inclusion/exclusion criteria. A total of 67 studies were included in this meta-analysis.

Tobacco metabolizing related genes

GST genes

Among 30 studies on the *GSTM1* polymorphism in Table 2, the results showed the *GSTM1* null genotype increased the four digestive cancers risk (OR=1.118, 95% CI 1.022–1.222). No significant publication bias was found using Begg's test (p=0.10), while there was publication bias by Egger's test (p=0.045). According to the trim and fill analysis, the adjusted estimated effect was OR 1.054 (95% CI: 0.954-1.163) based on the random-effects model. Substantial heterogeneity was observed in this analysis (Q=70.248, p=0.000, I^2= 53.024 %), which suggested that *GSTM1* polymorphisms have different effects on the risk of four cancers, depending on the cancer type and ethnicity. Subgroup analysis based on ethnicity revealed that such an association was observed among both African (OR=1.614, 95% CI 1.038-2.51; I^2=0%, p for heterogeneity=1) and Asian (OR=1.284, 95% CI 1.122-1.47; I^2=57.181%, p for heterogeneity=0.001) populations; further subgroup analysis based on the cancer type showed that the *GSTM1* null genotype were associated with an increased risk of oesophageal cancer (OR=1.406, 95% CI 1.124-1.759; I^2=63.644%, p for heterogeneity=0.027) and gastric cancer (OR=1.335, 95% CI 1.145-1.556; I^2=52.921%, p for heterogeneity=0.019). Stratified analysis by smoking status showed the association of the *GSTM1* null genotype with the four cancers risk was significant among smokers (OR=1.179, 95% CI 1.030-1.349; I^2=57.328%, p for heterogeneity=0). In subgroup analyses among smokers, there was publication bias (p_{Begg} =0.004; p_{Egger} =0.029). According to the trim and fill analysis, the adjusted estimated effect was OR 1.012 (95%CI: 0.867-1.181) based on the random-effects

model. However, the effect size was only found in Asian population (OR=1.355, 95% CI 1.089-1.686; I^2=39.566%, *p* for heterogeneity=0.044). Smokers with the *GSTM1* null genotype had an increased risk of oesophageal cancer (OR=1.382, 95% CI 1.009-1.894, I^2=55.082, *p* for heterogeneity=0.064) and gastric cancer (OR=1.690, 95% CI 1.298-2.201, I^2=69.955%, *p* for heterogeneity=0). Moreover, subgroup analyses in non-smokers showed that the *GSTM1* null genotype also increased the gastric cancer risk (OR=1.344, 95% CI 1.054-1.715; I^2=51.576%, *p* for heterogeneity=0.024). The *GSTM1* null genotype was associated with the four cancers risk in Asian population (OR=1.237, 95% CI 1.020-1.500; I^2=44.307%, *p* for heterogeneity=0.023), no publication bias was observed (*p*>0.05).

Table 1: Characteristics of included case-control studies

First author, year	NOS	Country/Ethnicity	Cancer site	Genes	Genotype distribution (cases/controls)		Genotype distribution by smoking status (cases/controls)			
					No risk*	At risk$	Non-smoker		Smoker	
							No risk*	At risk$	No risk*	At risk$
Wang,2004	7	China/Asia	Oesophagus	*GSTM1*	53/57^	74/44	24/37	33/26	29/20	41/18
Rudolph,2012	8	German/Europe	Colorectum	*GSTM1*	822/844	932/923	368/424	425/466	404/382	458/417
				GSTT1	1,433/1,459	313/308	644/722	142/170	715/672	147/123
Lilla,2007	9	Germany/Europe	Colorectum	*SULT1A1*	212/263	292/340	106/132	132/157	106/131	160/183
Gao,2002	9	China/Asia	Oesophagus	*GSTM1*	35/90	106/133	13/38	36/58	22/52	70/75
				GSTT1	67/104	74/119	20/44	29/52	47/60	45/67
			Stomach	*GSTM1*	63/90	90/133	10/38	20/58	53/52	70/75
				GSTT1	82/104	71/119	20/44	10/52	62/60	61/67
Dandara,2006	7	South Africa/Africa	Oesophagus	*SULT1A1*	115/132	121/134	27/41	28/47	88/91	93/87
Li,2010	7	South Africa/Africa	Oesophagus	*GSTM1*	206/200	133/80	55/75	8/20	151/125	125/60
				GSTT1	127/178	113/102	27/66	36/29	100/112	77/73
				GSTP1	92/107	148/173	21/30	42/65	71/77	106/108
Gertig,1998	7	America/Americas	Colorectum	*GSTM1*	97/104	114/117	36/40	41/40	61/64	73/77
				GSTT1	173/169	36/51	61/60	16/19	112/109	20/32
Tiemersma,2004	7	Netherlands/Europe	Colorectum	*GSTM1*	203/206	228/226	81/102	85/118	119/103	143/108
				GSTT1	370/363	61/69	139/177	27/43	228/185	34/26
				NAT2	262/254	169/178	89/132	66/67	169/121	79/77
				SULT1A1	149/169	282/263	66/97	72/97	83/62	128/106
Abo-Hashem,2016	7	Egypt/Africa	Liver	*GSTP1*	23/31	17/9	11/27	9/3	12/4	8/6
Li,2005	6	China/Asia	Stomach	*GSTM1*	33/36	67/26	16/23	30/19	17/13	37/7
Tsukino,2004	7	Japan/Asia	Stomach	*hOGG1*	32/74	110/197	11/38	39/99	21/36	71/98
Inoue,2000	7	Japan/Asia	Colorectum	*GSTM1*	97/97	108/123	19/37	17/36	78/60	91/87
				CYP1A1&	86/87	119/133	14/20	22/53	72/67	97/80
Lee,2000	7	China/Asia	Oesophagus	*GSTP1*	65/160	25/94	11/98	11/50	54/55	14/40
Shen,2005	7	China/Asia	Stomach	*GSTM1*	41/314	71/361	31/302	54/345	10/12	17/16
				CYP1A1#	70/412	42/264	57/391	29/254	13/21	13/10
Yoshida,2007	7	Japan/Asia	Colorectum	*GSTM1*	30/59	36/62	20/26	15/29	8/29	18/32
				CYP1A1#	34/79	32/42	20/36	15/19	14/40	12/21
				CYP1A1&	20/49	46/72	8/24	27/31	12/23	14/38
				NAT2	2/9	64/112	0/5	35/50	1/4	25/57
Zendehdel,2009	9	Sweden/Europe	Oesophagus	*GSTM1,*	52/230	43/239	17/112	13/87	35/127	30/143
				GSTT1	80/394	15/76	24/173	6/26	56/221	9/49
				GSTP1	44/208	50/245	13/82	16/110	31/126	34/135
			Oesophagus	*GSTM1,*	35/230	42/239	4/112	4/87	30/127	38/143
				GSTT1	70/394	7/76	8/173	1/26	62/221	6/49
				GSTP1	26/208	52/245	5/82	5/110	21/126	47/135
			Stomach	*GSTM1,*	54/230	70/239	6/112	8/87	4/127	62/143
				GSTT1	111/394	13/76	12/173	2/26	99/221	11/49
				GSTP1	47/208	75/245	6/82	8/110	41/126	67/135
Lee,2006	7	Chile/Americas	Stomach	*GSTM1,*	60/207	13/56	29/128	2/33	31/79	11/23
				CYP1A1&	38/153	35/110	16/90	15/71	22/63	20/39
Huang,2006	9	America/Americas	Colon	*GSTM1*	297/503	257/371	111/211	97/151	184/292	158/219
				GSTT1	428/603	130/271	162/247	46/115	259/356	83/155
Moore,2005	7	U.S./Americas	Colorectum	*GSTM1*	311/313	352/376	105/122	115/150	190/173	217/205
				GSTT1	561/584	129/118	182/230	44/50	350/325	77/56
				GSTP1	282/317	399/381	97/132	123/140	173/171	251/251
Cai,2001	8	China/Asia	Stomach	*GSTM1*	35/51	60/43	12/28	22/32	23/23	38/11
Tamer,2005	7	Turkey/Asia	Stomach	*GSTM1*	30/116	40/88	17/75	19/45	13/41	21/43
				GSTT1	49/151	21/53	25/85	11/35	24/66	10/18
				GSTP1	38/90	32/114	20/49	16/71	18/41	16/43
Slattery,2002	7	USA/Americas	Colon	*GSTM1*	761/892	816/1012	332/413	326/486	429/479	490/526
				NAT2	920/1154	688/804	366/540	298/380	554/614	390/424
García-González,2012	8	Spain/Europe	Stomach	*GSTM1*	274/290	283/267	125/151	120/147	51/40	71/35
				GSTT1	437/440	120/117	188/228	57/70	97/56	25/19
				GSTP1	255/251	302/306	119/138	126/160	50/36	72/39
Malik,2010	8	India/Aisa	Stomach	*hOGG1*	50/94	58/101	15/68	17/79	35/21	40/17

First author, year	NOS	Country/Ethnicity	Cancer site	Genes	Genotype distribution (cases/controls)		Genotype distribution by smoking status (cases/controls)			
					No risk*	At risk$	Non-smoker		Smoker	
							No risk*	At risk$	No risk*	At risk$
Malik,2009	7	India/Asia	Stomach	*GSTM1*	44/116	64/79	12/85	20/62	32/26	43/12
Slattery,2003	9	US/Americas	Rectum	*GSTM1*	230/279	243/295	84/123	88/124	145/156	153/171
				NAT2	247/306	204/255	90/143	74/105	156/163	128/150
Kasahara,2008	7	Japan/Asia	Colorectum	*hOGG1*	17/39	51/82	8/14	28/41	7/23	19/37
				XRCC1	42/62	26/59	20/29	16/26	18/30	8/30
Wu,2003	6	China/Asia	Oesophagus	*SULT1A1*	135/274	52/34	44/153	25/19	91/121	27/15
Yu,1995	7	China/Asia	Liver	*GSTM1*	14/55	16/95	7/34	10/61	7/21	6/34
Yu,1999 a	7	China/ Asia	Liver	*GSTM1*	38/151	42/177	25/94	22/104	13/57	20/73
Yu,1999 b	7	China/Asia	Liver	*GSTM1*	42/159	42/216	26/91	23/132	16/67	19/84
				GSTT1	42/194	41/181	25/110	24/113	17/84	17/67
Moslehi,2006	6	USA/Americas	Colorectum	*NAT2*	413/376	272/317	140/158	92/124	249/195	168/168
Malakar,2012	9	India/Asia	Stomach	*GSTM1*	45/107	57/97	7/52	14/30	38/55	43/67
				GSTT1	65/111	37/93	11/45	10/37	54/66	27/56
Yu,2000	7	China/Asia	Liver	*NAT2*	27/55	124/156	16/30	59/100	11/25	65/56
Songserm,2014	8	Thailand/Asia	Liver	*hOGG1*	34/95	111/234	14/55	50/123	20/40	61/111
				XRCC1	4/21	156/318	2/11	70/170	2/10	86/148
Ates,2005	7	Turkey/Asia	Colorectum	*GSTM1*	83/116	98/88	44/75	46/45	39/41	52/43
				GSTT1	118/151	63/53	56/85	34/35	62/66	29/18
				GSTP1	73/90	108/114	30/49	60/71	43/41	47/43
Van der Hel,2003 a	8	Netherlands/Europe	Colorectum	*GSTM1*	124/396	88/369	73/271	65/257	51/125	23/112
				GSTT1	154/541	58/224	104/385	34/143	50/156	24/81
Van der Hel,2003 b	7	Netherlands/Europe	Colorectum	*NAT2*	146/495	112/362	99/341	63/249	42/153	45/113
Moaven,2010	7	Iran/Asia	Oesophagus	*GSTP1*	84/74	64/62	51/65	50/46	33/10	14/16
Zhang,2014	8	China/Asia	Colorectum	*hOGG1*	44/48	203/252	30/32	129/158	14/16	74/94
Ghosh,2016	9	India/Asia	Stomach	*GSTP1*	41/61	29/21	10/38	9/16	31/23	20/5
				XRCC1	28/48	42/34	8/33	11/21	20/15	31/13
Boccia,2005	7	Italy/Europe	Stomach	*SULT1A1*	40/160	36/100	33/126	24/83	7/31	10/15
Boccia,2015	7	Italy/Europe	Liver	*GSTM1*	96/139	105/150	31/91	48/81	62/48	57/69
				GSTT1	141/220	60/69	59/129	20/43	81/91	38/26
				CYP1A1&	165/226	56/64	65/136	20/37	98/90	35/27
				SULT1A1	132/180	89/110	52/103	33/70	78/77	55/40
Yuan,2012	8	China/Asia	Liver	*hOGG1*	67/144	283/256	30/48	83/84	37/96	200/172
Sakamoto,2006	7	Japan/Asia	Liver	*hOGG1*	56/73	153/202	35/56	105/152	21/17	48/50
Hanaoka,2001	8	Brazil/Americas	Stomach	*hOGG1*	133/123	75/82	72/85	48/55	61/38	27/25
Gelatti,2005	8	Italy/Europe	Liver	*GSTM1*	101/185	99/215	41/60	34/80	60/125	65/135
				GSTT1	168/328	32/72	67/124	8/16	101/204	24/56
				NAT2	105/201	95/199	40/65	35/75	65/136	60/124
Setiawan,2000	9	China/Asia	Stomach	*GSTM1*	45/207	42/212	26/131	18/143	19/76	24/69
				GSTT1	37/228	44/190	18/146	21/127	19/82	23/63
Setiawan,2001	9	China/Asia	Stomach	*GSTP1*	61/296	20/123	30/199	10/75	31/97	10/48
Zhang,2012	7	China/Asia	Stomach	*GSTP1*	331/343	219/207	69/136	37/77	82/100	59/71
Chen,2004	8	China/Asia	Colon	*GSTM1*	23/151	30/188	17/92	16/108	6/57	14/79
				GSTT1	41/270	12/69	26/153	7/47	15/116	5/20
			Rectum	*GSTM1*	33/151	39/188	23/92	26/108	10/57	13/79
				GSTT1	61/270	11/69	43/153	6/47	18/116	5/20
Bhat, 2014	7	India/Asia	Oesophagus	*CYP1A1*#	253/300	273/226	101/134	99/122	152/166	174/104
Chen, 2011	7	China/Asia	Stomach	*XRCC1*	177/132	157/202	83/88	67/124	94/44	90/78
Fernandes, 2016	8	Brazil/Americas	Colorectum	*CYP1A1*#	193/312	34/88	107/190	24/53	86/122	10/35
				CYP1A1&	165/246	62/154	96/156	35/87	69/90	27/67
Hou, 2005	7	USA/Americas	Colorectum	*CYP1A1*#	633/643	42/36	219/258	9/19	387/344	29/15
Li, 2009	7	China/Asia	Liver	*CYP1A1*#	560/598	410/402	313/320	223/212	247/278	187/190
Little, 2006	8	Northeast Scotland/Europe	Colorectum	*CYP1A1*#	235/372	16/24	75/128	5/5	84/142	7/10
				CYP1A1&	190/310	42/68	63/107	12/19	68/122	16/27
Malakar,2014	7	India/Asia	Stomach	*p53*	11/36	94/174	1/14	20/71	10/22	74/103
Qiu, 2016	6	China/Asia	Liver	*p53*	221/244	764/748	137/207	488/645	84/37	276/103
Shao, 2008	6	China/Asia	Oesophagus	*p53*	163/195	510/499	61/90	229/219	102/105	281/280
Shen,2004	7	China/Asia	Stomach	*p53*	96/94	228/223	36/46	97/76	60/48	131/147
Yan,2009	6	China/Asia	Stomach	*XRCC1*	241/345	214/305	121/186	91/163	106/155	111/136
Yang, 2008	7	China/Asia	Oesophagus	*p53*	373/273	62/277	222/200	43/200	151/73	19/77
Yu, 1999 c	9	China/Asia	Liver	*CYP1A1*#	46/239	35/170	33/147	15/97	13/92	20/73
				CYP1A1&	25/152	56/257	19/86	29/158	6/66	27/99
Yu,2004	7	China/Asia	Oesophagus	*XRCC1*	65/88	70/64	33/50	28/35	32/38	42/29
Cai, 2017	7	China/Asia	Liver	*p53*	63/65	279/282	33/55	146/171	30/10	133/111
Putthanachote, 2017	7	Putthanachote/ Asia	Stomach	*XRCC1*	12/8	89/194	8/3	41/105	4/5	48/89

Aberrations: NOS, the Newcastle-Ottawa-Scale.

^Number of cases and controls.

*The wild type of each gene.

$The mutant type of each gene.

For *CYP1A1*, the Ile462Val substitution (Ile/Val+Val/Val).

& For *CYP1A1*, the 3801T>C substitution (MspI) (T/C+C/C).

Table 2: Meta-analysis of the association between *GSTM1*, *GSTT1* polymorphisms and the four digestive cancers risk

Stratified analysis	Subgroup analysis	No. of studies	OR (95% CI)	Heterogeneity test			Publication bias	False-positive report probability	Statistical power
				Q	P	I^2 (%)	*p*		
GSTM1 total population	Overall cancer	30	**1.118(1.022-1.222)**	70.248	0	53.024	0.100*	0.050	0.659
	Cancer type						0.045§		
	Colorectum	12	1.010(0.911-1.121)	11.808	0.461	0			
	Oesophagus	4	**1.406(1.124-1.759)**	11.002	0.027	63.644		0.047	0.337
	Stomach	11	**1.335(1.145-1.556)**	21.241	0.019	52.921		0.048	0.991
	Liver	5	0.866(0.691-1.086)	1.763	0.779	0			
	Ethnicity								
	Africa	1	**1.614(1.038-2.51)**	0	1	0		0.042	0.782
	Americas	6	1(0.853-1.172)	3.552	0.616	0			
	Asia	17	**1.284(1.122-1.47)**	39.702	0.001	57.181		0.048	0.976
	Europe	7	0.991(0.862-1.141)	7.724	0.461	0			
GSTM1 non-smokers	Overall cancer	30	1.071(0.948-1.210)	54.333	0.011	39.263	0.486*		
	Cancer type						0.186§		
	Colorectum	12	0.993(0.847-1.163)	10.507	0.572	0			
	Oesophagus	4	1.250(0.826-1.891)	6.091	0.192	34.331			
	Stomach	11	**1.344(1.054-1.715)**	20.651	0.024	51.576		0.047	0.716
	Liver	5	0.866(0.622-1.206)	8.996	0.061	55.538			
	Ethnicity								
	Africa	1	0.545(0.207-1.435)	0	1	0			
	Americas	6	0.956(0.759-1.205)	7.012	0.220	28.698			
	Asia	17	**1.237(1.020-1.500)**	30.524	0.023	44.307		0.048	0.542
	Europe	7	1.018(0.828-1.253)	8.301	0.405	3.625			
GSTM1 smokers	Overall cancer	30	**1.179(1.030-1.349)**	77.335	0	57.328	0.004*	0.050	0.728
	Cancer type						0.029§		
	Colorectum	12	1.014(0.855-1.203)	12.204	0.429	1.673			
	Oesophagus	4	**1.382(1.009-1.894)**	8.905	0.064	55.082		0.046	0.301
	Stomach	11	**1.690(1.298-2.201)**	33.284	0	69.955		0.047	0.999
	Liver	5	0.862(0.606-1.227)	3.146	0.534	0			
	Ethnicity								
	Africa	1	1.725(0.891-3.339)	0	1	0			
	Americas	6	1.035(0.794-1.349)	1.146	0.950	0			
	Asia	17	**1.355(1.089-1.686)**	28.106	0.044	39.566		0.048	0.755
	Europe	7	1.054(0.826-1.343)	37.431	0	78.628			
GSTT1 total population	Overall cancer	18	0.970(0.863-1.092)	38.800	0.010	45.876	0.150*		
	Cancer type						0.628§		
	Colorectum	8	0.935(0.782-1.119)	17.558	0.025	54.438			
	Oesophagus	3	1.068(0.778-1.466)	7.426	0.060	59.599			
	Stomach	6	0.923(0.722-1.180)	8.715	0.121	42.626			
	Liver	3	1.084(0.772-1.521)	2.108	0.348	5.136			
	Ethnicity								
	Africa	1	1.553(0.978-2.465)	0	1	0			
	Americas	3	0.827(0.643-1.063)	8.377	0.015	76.124			
	Asia	8	1.017(0.837-1.237)	11.380	0.181	29.703			
	Europe	8	0.950(0.805-1.122)	8.447	0.391	5.297			
GSTT1 non-smokers	Overall cancer	18	0.979(0.838-1.143)	28.943	0.115	27.443	0.554*		
	Cancer type						0.610§		
	Colorectum	8	0.881(0.752-1.031)	9.792	0.280	18.297			
	Oesophagus	3	**1.845(1.204-2.829)**	4.065	0.255	26.196		0.043	0.999
	Stomach	6	0.973(0.732-1.293)	4.639	0.462	0			
	Liver	3	0.965(0.649-1.436)	0.047	0.977	0			
	Ethnicity								
	Africa	1	**3.034(1.564-5.889)**	0	1	0		0.040	0.909
	Americas	3	0.797(0.605-1.051)	3.882	0.144	48.487			
	Asia	8	0.999(0.779-1.280)	9.695	0.287	17.481			
	Europe	8	0.944(0.801-1.112)	1.915	0.984	0			
GSTT1 smokers	Overall cancer	18	0.977(0.843-1.132)	31.747	0.062	33.852	0.888*		
	Cancer type						0.996§		
	Colorectum	8	1.043(0.834-1.305)	13.100	0.108	38.930			
	Oesophagus	3	0.858(0.593-1.240)	4.475	0.215	32.963			
	Stomach	6	0.844(0.615-1.159)	8.526	0.130	41.354			
	Liver	3	1.192(0.778-1.825)	2.556	0.279	21.741			
	Ethnicity								
	Africa	1	1.181(0.638-2.186)	0	1	0			
	Americas	3	0.864(0.606-1.232)	6.401	0.041	68.754			
	Asia	8	1.117(0.844-1.478)	10.680	0.221	25.093			
	Europe	8	0.907(0.710-1.158)	12.237	0.141	34.627			

The bold letters show statistically significant results.

* Begg's test for publication bias.

§ Egger's test for publication bias.

Among 18 studies on the *GSTT1* polymorphism in Table 2, we found that the *GSTT1* null genotype could increase the oesophageal cancer risk in non-smokers (OR=1.845, 95% CI 1.204-2.829; I^2=26.196%, *p* for heterogeneity=0.255). By subgroup analysis in non-smokers, Only one study showed the *GSTT1* polymorphisms were related to the risk of four cancers in African population (OR=3.034, 95% CI 1.564-5.889)[22]. No publication bias was detected in this analysis (p>0.05).

Among 12 studies on the *GSTP1* polymorphism in Supplementary Table S1, no significant correlations were found except one study on liver cancer in non-smokers (OR=7.364, 95% CI 1.671-32.440)[49]. There was no publication bias (p>0.05).

CYP1A1 gene

Eight papers provided data on the *CYP1A1* Ile462Val polymorphism in Table 3. The results indicated that smokers with the *CYP1A1* Ile462Val polymorphisms were at an increased risk of four cancers in Asian population (OR=1.585, 95%CI 1.029-2.442; I^2=41.870%, *p* for heterogeneity=0.142). Seven articles were about *CYP1A1* MspI polymorphism in Supplementary Table S1. The *CYP1A1* MspI polymorphisms were not associated with the risk of four cancers in stratified analysis and subgroup analysis.

SULT1A1 gene

In Table 3, the *SULT1A1* slow/intermediate phenotypes were associated with a 31.5% increase in the risk of four cancers (OR=1.315, 95% CI 1.009-1.715) from 6 studies. However, such an association was not observed in stratified analysis and subgroup analysis. Only one paper showed the association was significant in Asian population (OR=3.104, 95% CI 1.923-5.011)[64].

NAT2 gene

Eight papers provided data on the *NAT2* polymorphism, as shown in Table 4. Two studies indicated that the *NAT2* polymorphism was associated with the risk of four cancers in Asian population (OR=1.701, 95% CI 1.019-2.838) [28, 60]. Moreover, the association was also observed in smokers (OR=2.513, 95% CI 1.156-5.462).

DNA repair genes

Neither *hOGG1* gene nor *XRCC1* gene polymorphism was not associated with the risk of four cancers, as shown in Supplementary Table S1.

Tumour suppressor gene

We also found no significant association of *p53* polymorphism with the risk of four cancers (Supplementary Table S1).

Discussion

A total of 67 case-control studies on the interaction of gene-smoking on the risk of four digestive cancers were identified in this review. This study included six tobacco metabolizing genes (*GSTM1*, *GSTT1*, *GSTP1*, *CYP1A1*, *SULT1A1*, and *NAT2*), two DNA repair genes (*hOGG1* and *XRCC1*) and one tumour suppressor gene (*p53*). To the best of our knowledge, this is the first meta-analysis that investigated the joint effect of the most gene polymorphisms and smoking on four digestive cancers. Our data indicated the GSTM1 polymorphism was associated with the risk of four digestive cancers among Asian population (OR 1.284, 95% CI: 1.122-1.470). The *GSTM1* null genotype could increase the gastric cancer risk (OR 1.335, 95% CI: 1.145-1.556) in total population. However, the association of the *GSTM1* null genotype with the oesophageal cancer risk was found in smokers (OR 1.382, 95% CI: 1.009-1.894), not in non-smokers (OR 1.250, 95% CI: 0.826-1.891). Interestingly, we found the GSTT1 null genotype could increase the oesophageal cancer risk among non-smokers in only 3 studies (OR 1.845, 95% CI: 1.204-2.829). The *SULT1A1* polymorphism was related to the risk of four digestive cancers (OR 1.315, 95% CI: 1.009-1.715), but such an association was not observed in stratified analysis and subgroup analysis except one study in Asian population (OR=3.104, 95% CI 1.923-5.011). Two studies indicated that the *NAT2* polymorphism was associated with the risk of four cancers in Asian population (OR=1.701, 95% CI 1.019-2.838), and the association was also observed in smokers (OR=2.513, 95% CI 1.156-5.462). Moreover, smokers with the *CYP1A1* Ile462Val polymorphism were at an increased cancer risk in Asian population (OR=1.585, 95% CI 1.029-2.442). None of the other gene-smoking interactions was observed in the above cancers.

Increasing studies investigated the gene–smoking interaction on the risk of cancer during these years. Two previously published studies indicated smokers with *GSTM1* null genotype were at an increased oesophageal cancer risk [19, 21]. Moreover, the significant association was found between *CYP1A1* Ile462Val and liver cancer risk among the cigarette smoking subjects in a meta-analysis (OR = 1.40, 95% CI 1.06-1.85) [84]. These results were similar to our findings. Zhang *et al* indicated the *NAT2* polymorphisms were correlated to an increased liver cancer risk in smokers [11]. Whereas our study only provided two studies to support this conclusion. The *SULT1A1* Arg213His polymorphism was associated with an increased

oesophageal cancer risk [85], but such an association was not founded in our subgroup analysis. We also found no interaction of smoking with other genetic polymorphisms on four digestive cancers. Several reasons account for the null results.

First, the association between gene polymorphism and cancer risk could be modified by various smoking habits, including the age of initiating smoking, duration of smoking, pack-years of smoking, the method of tobacco use and cigarette categories. One study showed that lifetime exposure to tobacco increased the risk of upper aero-digestive tract (UADT) cancers. Furthermore, chewing tobacco was more likely to increase the risk of UADT cancers (OR=7.61; 95% CI 4.65-12.45) compared to smoking [86]. The categories of cigarette also play a role in cancer progression and affect the association of gene polymorphisms with cancer susceptibility [87]. Remarkably, Liang *et al* reported on the significant interactions of smoking pack years with *HEL*308 genotypes ($P_{interaction}$=0.026) and *ADH1B* genotypes ($P_{interaction}$=0.0016) in the head and neck squamous cell carcinoma (HNSCC) risk, respectively [88]. Most of the included studies only provided data to evaluate the smoking status and we could not verify the findings in our study. Moreover, the age of initiating smoking is rarely measured in published studies, but this factor could be related to genetic polymorphisms in subgroups. Second, many other genes could be relevant to the metabolism of harmful compounds in tobacco except for the included genes, and the gene-gene interaction also existed in cancer susceptibility [89, 90]. It is probable that combinations of multiple gene polymorphisms are more significant as risk factors than a single gene polymorphism.

Interestingly, we found the *GSTT1* null genotype could increase oesophageal cancer risk among non-smokers, but not among smokers. It was conflictive with the recognized conclusion on tobacco use increasing the cancer risk. However, this result also suggested not all the smokers with high-risk genetic variants were at an increased cancer risk. Because other benefical environmental factors, such as dietary habits, play an important role in cancer prevention [91]. A previous study indicated that regular tea consumption decreased the OC (OR: 0.38, 95% CI: 0.17–0.87) and GC (OR: 0.30, 95% CI: 0.14–0.66) risk among those with *GSTT1* null genotype [21]. Ko *et al* also showed soy product consumption was associated with lower breast cancer risk in BRCA mutation carriers (HR: 0.39; 95% CI: 0.19-0.79) [92]. It was resonalble to assume that a protective factor also interacted with the *GSTT1* null genotype among smokers. Moreover, our finding was based on only 3 papers, and needed to be further verified by more studies.

Regarding the interaction between smoking and *GSTM1* and *CYP1A1* IIe462Val on digestive cancers risk, evidence regarding the molecular mechanism also supported the results of this meta-analysis. Tobacco smoke contains various carcinogens, for example, polycyclic aromatic hydrocarbons (PAHs) and tobacco specific nitrosamines (TSNA) [93]. These carcinogens are first metabolically activated by phase I enzymes, e.g., cytochrome P4501A1 (CYP1A1), into their final forms and then combine with DNA, forming aromatic-DNA adducts that are considered as an early stage in carcinogenesis. Moreover, these activated forms are detoxified by phase II enzymes, especially glutathione S-transferases (GSTs)[94]. Thus, the susceptibility to cancer determined by genetic factors may depend on the metabolic balance between phase I and phase II enzymes[8]. Because the CYP and GST genetic polymorphisms regulate the metabolism of xenobiotics, they are thought to affect individual's sensitivity to environmental factors and susceptibility to cancer. Although this meta-analysis suggested that there was no significant interaction between smoking and other gene polymorphisms, several related molecular mechanisms remain biologically plausible. Except for the CYP and GST family genes, the carcinogens in tobacco smoke can be activated by *SULT1A1* and *NAT2* [95, 96]. DNA repair genes, e.g, *hOGG1* and *XRCC*, are involved in the elimination of DNA adducts, which suggests that the DNA repair genes polymorphisms may be associated with different repair efficiencies of DNA damage [69]. Moreover, the *p53* is a tumour suppressor gene and plays a key role in regulating the cell cycle and maintaining genomic integrity [79]. Thus, it may modify individual's susceptibility to various carcinogens.

Compared with a single study that investigated the role of some metabolic gene polymorphisms in cancer risk, we evaluated the interaction between ten gene polymorphisms and smoking for four digestive cancers, and this is the first such report to date. Therefore, we could provide more comprehensive information on the gene-smoking interaction in main digestive cancers. However, there are several limitations in this meta-analysis. First, there is strong heterogeneity in the risk estimates for most gene polymorphisms and stratified analyses. Second, the ORs were only adjusted for the cancer type and ethnicity. A more precise analysis should be performed based on the data adjusted for confounding factors including the age, sex, family history, environmental factors, cancer stage, and lifestyle. In addition, we were not able to evaluate the interaction of genes with genes or other

environmental factors, which should be assessed in future studies.

Table 3: Meta-analysis of the association between *CYP1A1*, *SULT1A1* polymorphisms and the four digestive cancers risk

Stratified analysis	Subgroup analysis	No. of studies	OR (95% CI)	Heterogeneity test			False-positive report probability	Statistical power
				Q	P	I^2 (%)		
CYP1A1 IIe462Val total population	Overall cancer	8	1.102(0.911-1.332)	13.969	0.052	49.888		
	Cancer type							
	Colorectum	4	1.039(0.724-1.490)	8.418	0.038	64.360		
	Oesophagus	1	1.432(0.829-2.474)	0	1	0		
	Stomach	1	0.936(0.494-1.776)	0	1	0		
	Liver	2	1.082(0.714-1.639)	0.005	0.945	0		
	Ethnicity							
	Americas	2	0.851(0.572-1.267)	3.949	0.047	74.676		
	Asia	5	1.197(0.961-1.492)	6.270	0.180	36.201		
	Europe	1	1.055(0.505-2.207)	0	1	0		
CYP1A1 IIe462Val non-smokers	Overall cancer	8	0.973(0.827-1.145)	6.539	0.478	0		
	Cancer type							
	Colorectum	4	0.901(0.586-1.384)	3.519	0.318	14.759		
	Oesophagus	1	1.077(0.647-1.792)	0	1	0		
	Stomach	1	0.783(0.434-1.412)	0	1	0		
	Liver	2	0.964(0.665-1.397)	1.531	0.216	34.681		
	Ethnicity							
	Americas	2	0.720(0.460-1.127)	0.539	0.463	0		
	Asia	5	1.009(0.846-1.204)	3.349	0.501	0		
	Europe	1	1.707(0.478-6.089)	0	1	0		
CYP1A1 IIe462Val smokers	Overall cancer	8	1.341(0.959-1.876)	17.436	0.015	59.853		
	Cancer type							
	Colorectum	4	1.067(0.565-2.015)	9.278	0.026	67.667		
	Oesophagus	1	1.827(0.658-5.075)	0	1	0		
	Stomach	1	2.100(0.494-8.926)	0	1	0		
	Liver	2	1.385(0.636-3.014)	1.846	0.174	45.832		
	Ethnicity							
	Americas	2	0.883(0.431-1.807)	8.182	0.004	87.778		
	Asia	5	**1.585(1.029-2.442)**	6.881	0.142	41.870	0.046	0.932
	Europe	1	1.183(0.341-4.108)	0	1	0		
SULT1A1 total population	Overall cancer	6	**1.315(1.009-1.715)**	17.371	0.004	71.216	0.048	0.993
	Cancer type							
	Colorectum	2	1.137(0.649-1.994)	0.502	0.478	0		
	Oesophagus	2	1.724(0.940-3.163)	13.122	0	92.379		
	Stomach	1	1.440(0.579-3.579)	0	1	0		
	Liver	1	1.103(0.480-2.536)	0	1	0		
	Ethnicity							
	Africa	1	1.036(0.730-1.472)	0	1	0		
	Asia	1	**3.104(1.923-5.011)**	0	1	0	0.044	0.997
	Europe	4	1.148(0.984-1.339)	1.332	0.722	0		
SULT1A1 non-smokers	Overall cancer	6	1.257(0.849-1.861)	17.039	0.004	70.656		
	Cancer type							
	Colorectum	2	1.068(0.494-2.311)	0.021	0.885	0		
	Oesophagus	2	2.027(0.853-4.819)	10.933	0.001	90.853		
	Stomach	1	1.104(0.339-3.591)	0	1	0		
	Liver	1	0.934(0.296-2.947)	0	1	0		
	Ethnicity							
	Africa	1	0.905(0.461-1.776)	0	1	0		
	Asia	1	**4.575(2.308-9.070)**	0	1	0	0.041	0.991
	Europe	4	1.045(0.836-1.307)	0.242	0.970	0		
SULT1A1 smokers	Overall cancer	6	1.248(0.952-1.637)	8.766	0.119	42.964		
	Cancer type							
	Colorectum	2	0.996(0.660-1.501)	0.439	0.507	0		
	Oesophagus	2	1.454(0.893-2.369)	3.562	0.059	71.922		
	Stomach	1	2.952(0.864-10.091)	0	1	0		
	Liver	1	1.357(0.688-2.680)	0	1	0		
	Ethnicity							
	Africa	1	1.105(0.652-1.875)	0	1	0		
	Asia	1	**2.393(1.117-5.126)**	0	1	0	0.040	0.694
	Europe	4	1.146(0.854-1.539)	4.358	0.225	31.169		

The bold letters show statistically significant results.

Table 4: Meta-analysis of the association between *NAT2* polymorphism and the four digestive cancers risk

Stratified analysis	Subgroup analysis	No. of studies	OR (95% CI)	Heterogeneity test			False-positive report probability	Statistical power
				Q	P	I^2 (%)		
total population	Overall cancer	8	0.990(0.872-1.125)	11.662	0.112	39.978		
	Cancer type							
	Colorectum	6	0.970(0.837-1.123)	7.981	0.157	37.351		
	Liver	2	1.115(0.796-1.561)	3.280	0.070	69.515		
	Ethnicity							
	Americas	3	0.961(0.832-1.109)	6.101	0.047	67.219		
	Asia	2	**1.701(1.019-2.838)**	0.303	0.582	0	0.044	0.426
	Europe	3	0.963(0.793-1.168)	0.553	0.759	0		
non-smokers	Overall cancer	8	1.047(0.889-1.232)	8.934	0.257	21.649		
	Cancer type							
	Colorectum	6	1.072(0.894-1.285)	7.483	0.187	33.179		
	Liver	2	0.886(0.556-1.414)	0.695	0.404	0		
	Ethnicity							
	Americas	3	1.044(0.802-1.359)	2.478	0.290	19.295		
	Asia	2	1.251(0.597-2.622)	1.607	0.205	37.779		
	Europe	3	1.004(0.730-1.382)	4.444	0.108	54.996		
smokers	Overall cancer	8	0.993(0.817-1.205)	13.717	0.056	48.968		
	Cancer type							
	Colorectum	6	0.933(0.755-1.152)	7.364	0.195	32.101		
	Liver	2	1.334(0.837-2.125)	4.334	0.037	76.927		
	Ethnicity							
	Americas	3	0.913(0.749-1.113)	2.470	0.291	19.037		
	Asia	2	**2.513(1.156-5.462)**	0.113	0.737	0	0.040	0.379
	Europe	3	0.988(0.745-1.310)	4.613	0.100	56.648		

The bold letters show statistically significant results.

In summary, our meta-analysis provides the evidence of two potential gene-smoking interactions, one is between smoking and *GSTM1* on oesophageal cancer, and the other is between smoking and *CYP1A1* Ile462Val on the four cancers in Asian populations. None of the other gene-smoking interactions was observed in the above cancer. Future studies need to be conducted to verify the conclusions.

Supplementary Material

Supplementary table S1.
http://www.jcancer.org/v09p1506s1.pdf

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Competing Interests

The authors have declared that no competing interest exists.

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