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Research Paper

Association of MUC1 rs4072037 Functional Polymorphism and Cancer Risk: Evidence from 12551 Cases and 13436 Controls

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Abstract

Objectives: The result of the relationship between the MUC1 rs4072037 polymorphism and cancer risk is controversial, we take this meta-analysis to investigate a more precise result.

Methods: Electronic database Pubmed, Web of science and Cochrane library had been used to search relevant articles concerning the relationship between MUC1 rs4072037 polymorphism and cancer risk. We used odds ratios (ORs) and 95% confidence intervals (CIs) to assess the strength of the gene-disease association. We also conducted subgroup analysis, sensitivity analyses and publication bias in the meta-analysis.

Results: In our meta-analysis, we involved 17 studies (19 datasets) with 12551 cases and 13436 controls eventually. It showed the MUC1 rs4072037 polymorphism was associated with decreased cancer risk in four genetic models (G *vs.* A: OR=0.79, 95%CI: 0.71-0.89, *P*< 0.001; AG *vs.* AA: OR=0.72, 95%CI: 0.62-0.82, *P*< 0.001; GG *vs.* AA: OR=0.78, 95%CI: 0.69-0.88, *P*< 0.001; AG+GG *vs.* AA: OR=0.72, 95%CI: 0.63-0.83, *P*< 0.001). In subgroup analysis, it showed a decreased cancer risk among Asians but not Caucasians and a significant decreased gastric cancer risk in all genetic models.

Conclusion: MUC1 rs4072037 polymorphism is associated with decreased cancer risk and can probably be used as a tumor marker, especially for gastric cancer and for Asians.

Key words: Cancer, MUC1 rs4072037, Polymorphism, Meta-analysis

Introduction

Cancer is the main disease lead to death in the world. Approximately 14.1 million cancer cases occurred and 8.2 million cancer patients died in 2012[1]. Gastric cancer is the fourth most common cancer worldwide. It is also the second leading cause of cancer death. Every year, there are more than 950000 new gastric cancer patients [2]. Cancer is a complex disease. Endogenous factors (genetic, immune and endocrine disorders) and exogenous factors (unhealthy behaviors and environmental carcinogens) are both contributed to the cause of cancer [3]. However, under similar environmental circumstances, some people have cancers while others not may suggest genetic predisposition is vital in cancer development.

Single nucleotide polymorphisms (SNPs) are signal-base pairs in genomic DNA that vary in at least 1% of the population [4] and account for much of normal human genetic variation [5]. SNPs which have relationship with cancer are involved in lots of cellular pathways related to DNA repair, cell proliferation, apoptosis, chemotherapy targets and immune response [6]. Recently, genome-wide association study (GWAS) was used to identify the

potential candidates for SNPs. Abnet et al.conducted a GWAS on Chinese population in 2010 and discovered MUC1 rs4072037 polymorphism was associated with the gastric cancer risk [7]. In 2011, Saeki et al. also found MUC1 rs4072037 polymorphism was associated with gastric cancer by the Japanese GC GWAS [8]. MUC1, or CA15.3, is expressed in epithelial linings in a different of tissues and is strongly expressed in the female genital tract during mammary gland and pregnancy and lactation [9]. Rs4072037, a functional SNP in exon 2 of the MUC1 gene, regulates splicing site selection during the posttranscriptional regulation process [10]. Besides gastric cancer, the MUC1 was also reported have association with colorectal cancer [11], ovarian cancer [12] and breast cancer [13]. But the consequences of these reports were controversial, we conducted this meta-analysis to evaluate a more precise association between the MUC1 rs4072037 polymorphism and cancer risk.

Materials and methods

Identification of Study

We searched Pubmed, Web of science and Cochrane library for relavant studies (updated to December, 2017). The search terms were " "Polymorphism, Single Nucleotide" or "Nucleotide Polymorphism, Single" or "Nucleotide Polymorphisms, Single" or "Polymorphisms, Single Nucleotide" or "Single Nucleotide Polymorphisms" or "SNPs" or "Single Nucleotide Polymorphism" " and " "Neoplasms" or "Neoplasia" or "Neoplasias" or "Neoplasm" or "Tumors" or "Tumor" or "Cancer" or "Cancers" or "Malignant Neoplasms" or "Malignant Neoplasm" or "Neoplasm, Malignant" or "Neoplasms, Malignant" or "Malignancy" or "Malignancies" or "Benign Neoplasms" or "Neoplasms, Benign" or "Benign Neoplasm" or "Neoplasm, Benign" " and " "MUC1" or "mucin1" or "1q22" ", with no language limited. In addition, in order to identify additional relevant studies, references of retrieved articles were also included in the manual review.

Criteria of selection

We selected studies according to these criteria: a. concerning the association between MUC1 rs4072037 and cancer risk. b. case-controls and cohort studies. c. identification of cancer was confirmed histologically. d. the number of each MUC1 rs4072037 genotype. e. genotype spreading of control compliance with Hardy-Weinberg equilibrium (HWE). When the same researcher had two or more publications covering the same patient population, the largest number study was included. There are major reasons for excluded the studies: a. case only studies. b. review papers, case report. c. HWE of controls was < 0.05. d. not providing available genotype frequency. e. containing the data which have common characteristics.

Data extraction

The data of the studies was extracted by JX Feng and LY Liu independently. We extracted these information from studies: name of the first author, publication year, country of origin, ethnicity of cases and controls, type of study, type of cancer, genotyping method, source of controls, HWE of controls, number of cases and controls, frequencies of different genotypes (AA, AG and GG genotypes).

Quality assessment

According to the Newcastle–Ottawa Scale (NOS), FJX and LLY conducted quality assessment independently. When disagreement appeared, authors discussed to solve it. The score of study lower than 6 was considered as "low quality", otherwise was "high quality".

Statistical analysis

To evaluate the strength of association between MUC1 rs4072037 polymorphism and cancer risk, crude odds ratios (ORs) and 95% confidence intervals (CIs) were used. The *Z* test was used to identify the statistical significance of pooled ORs. We calculated the pooled odds ratios (ORs) for the allelic model (G allele *vs*. A allele), heterozygote model (GA *vs*. AA), homozygote model (GG *vs*. AA), dominant model (GG+AG *vs*. AA) and recessive model (GG *vs*. AA+AG), respectively. To test the heterogeneity among studies, we performed a Cochrane chi-square-bsaed Q-test. In order to evaluate the statistical, I^2 tests were used. To evaluate heterogeneity between studies, the I^2 index which expresses the percentage of the total variation across studies due to heterogeneity was calculated. I^2 values of 25%, 50% and 75% represents the low, median and high heterogeneity respectively. When I^2 >50%, the random effects (Dersimonian-Laird method) [14] was implemented to calculate overall OR value. Otherwise, I^2 ≤50%, the fixed effects model (Mantel-Haenszel method) [15] was implemented. To search the heterogeneity between studies, subgroup analyses based on civilization, country, type of cancer, genotyping method and sample size were performed. Begg's funnel plot and Egger's linear regression test [16] were used to evaluate publication bias. We conducted sensitivity analyses by removing each single dataset to explore the influence of the single dataset on the pooled ORs. We used Stata software (version 12.0, Stata Corp, College Station, USA) to perform statistical analysis. All *P* values were

two-sides and $P \leq 0.05$ were considered statistically significant.

Consequences

Studying features

The process of literature selection is shown in the **Figure 1**. A total 126 articles identified through database searching. After screening title, abstract or the whole text, 19 studies were evaluated for suitability. Then 2 studies were excepted due to genotype distributions of control inconsistent with HWE[17,18]. Finally, 17 studies (19 datasets) with 12551 cases and 13436 controls were involved in this meta-analysis[8,11-13,19-31]. These studies were all case-control designed. There were 13 gastric cancer studies, 2 colorectal cancer studies, 1 breast cancer study, 1 lung cancer study, 1 ovarian cancer study and 1 esophagus cancer study. There were 13 studies of Asian descendent, 6 studies of Caucasian descendent and 1 study of American descendent. There were 10 studies used the genotyping method of TaqMan, 2 used the MassARRAY, 1 used the PCR-SSPs, 1 used the SNPlex and 1 used the KASP. The other characteristic of the studies were shown in the **Table 1**.

Conclusions of Meta-analysis

The main consequences of this meta-analysis are shown in the **Table 2.** MUC1 rs4072037 polymorphism is associated with significant decreased cancer risk in four genetic models (G *vs.* A: OR=0.79, 95%CI: 0.71-0.89, *P*< 0.001 **Figure 2**; AG *vs.* AA: OR=0.72, 95%CI: 0.62-0.82, *P*< 0.001 **Figure 3**; GG *vs.* AA: OR=0.78, 95%CI: 0.69-0.88, *P*< 0.001 **Figure 4**; AG+GG *vs.* AA: OR=0.72, 95%CI: 0.63-0.83, *P*< 0.001 **Figure 5**).

The subgroup analysis results were shown in the **Table 3**. By subgroup analysis in ethnicity, a reduced risk of cancer was found in entire genetic models (G *vs.* A: OR=0.75, 95%CI: 0.65-0.87, *P*< 0.001; AG *vs.* AA: OR=0.72, 95%CI: 0.61-0.85, *P*< 0.001; GG *vs.* AA: OR=0.75, 95%CI: 0.64-0.89, *P*= 0.001; AG+GG *vs.* AA: OR=0.72, 95%CI: 0.61-0.85, *P*< 0.001; GG *vs.* AG+AA, OR=0.81, 95%CI: 0.69-0.96, *P*= 0.013) among Asian descendent. However no similar association was found among Caucasian descendent. Furthermore, significantly reduced gastric cancer risk was found in entire genetic models (G *vs.* A: OR=0.70, 95%CI: 0.63-0.78, *P*< 0.001; AG *vs.* AA: OR=0.64, 95%CI: 0.55-0.74, *P*< 0.001; GG *vs.* AA: OR=0.62, 95%CI: 0.53-0.73, *P*< 0.001; AG+GG *vs.* AA: OR=0.64, 95%CI: 0.55-0.73, *P*< 0.001; GG *vs.* AG+AA, OR=0.75, 95%CI: 0.64-0.87, *P*< 0.001). However, no similar association was discovered in colorectal cancer and other cancers (breast cancer, lung cancer, ovarian cancer and esophagus cancer). Stratification by country (China and Japan), genotyping methods (TaqMan and other methods) or sample size (<1000 and ≥ 1000 subjects) all showed MUC1 rs4072037 polymorphism associated with an decreased cancer risk in all genetic models except recessive model.

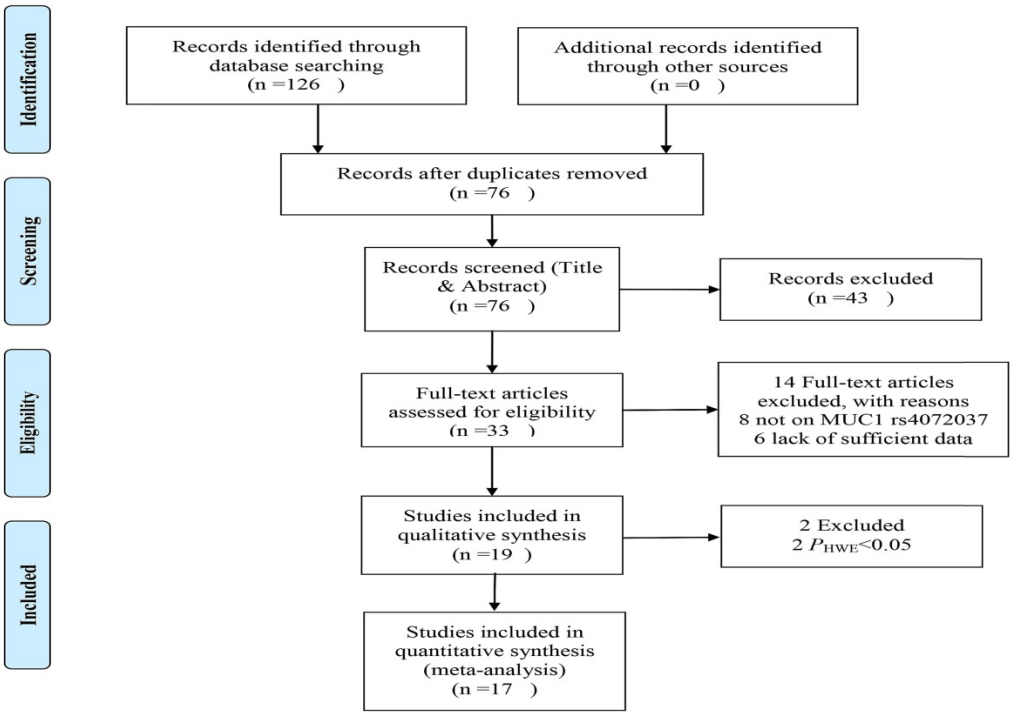

Figure 1. Flow diagram showing studying selection.

Table 1. Characteristics of included studies

Study	Year	Country	Ethnicity	Study-type	Cancer-type	Genotyping method	Source of control	Case	Control	P_{HWE}	NOS
Song[30]	2013	Korea	Asian	Case-control	GC	TaqMan	Population	3225	1697	0.279	6
Zhang H[24]	2011	China	Asian	Case-control	GC	TaqMan	Population	1658	1833	0.335	8
Kruit[13]	2009	Netherland	European	Case-control	BC	TaqMan	Population	229	208	0.985	6
Li F[19]	2012	China	Asian	Case-control	CRC	MassARRAY	Population	230	291	0.434	8
Kupcinskas[20]	2014	Lithuania	European	Case-control	GC	TaqMan	Population	249	232	0.284	6
Horimasu[21]	2017	Japan	Asian	Case-control	LC	TaqMan	Population	172	276	0.773	7
Yang[22]	2012	China	Asian	Case-control	GC	MassARRAY	Population	249	100	0.223	7
Zhang B[23]	2013	China	Asian	Case-control	GC	PCR-SSPs	Population	283	281	0.992	8
Kupcinskas[11]	2015	Lithuania	European	Case-control	CRC	TaqMan	Population	192	362	0.64	6
Palmer[17][a]	2013	Poland	European	Case-control	EC	TaqMan	Population	159	207	0.024	6
Palmer[17][a]	2013	Poland	European	Case-control	GC	TaqMan	Population	311	207	0.024	6
Cai[25]	2017	China	Asian	Case-control	GC	KASP	Population	480	488	0.975	6
Dai[26]	2014	China	Asian	Case-control	EC	TaqMan	Population	2072	2204	0.808	7
Jia[27]	2011	Poland	European	Case-control	GC	SNPlex	Population	272	376	0.483	7
Li M[28]	2013	China	Asian	Case-control	GC	TaqMan	Population	335	334	0.242	7
Williams[12]	2014	America	America	Case-control	OC	TaqMan	Population	727	757	0.939	6
Sun H[29]	2015	China	Asian	Case-control	GC	TaqMan	Hospital	692	774	0.735	7
Sun Y[31]	2014	America	European	Case-control	GC	TaqMan	Population	129	123	0.872	7
Qiu[18][a]	2016	China	Asian	Case-control	GC	TaqMan	Hospital	1124	1192	<0.001	7
Saeki-T[8]	2011	Japan	Asian	Case-control	GC	TaqMan	Population	605	1264	0.466	8
Saeki-A[8]	2011	Japan	Asian	Case-control	GC	TaqMan	Population	303	1467	0.11	8
Saeki-K[8]	2011	Korea	Asian	Case-control	GC	TaqMan	Population	449	369	0.391	8

[a]: Studies did not follow the HWE

GC: gastric cancer; BC: breast cancer; CRC: colorectal cancer; LC: lung cancer; EG: esophagus cancer; OC: ovarian cancer

T: Tokyo; A: Aichi; K: Korea

NOS: Newcastle–Ottawa Scale

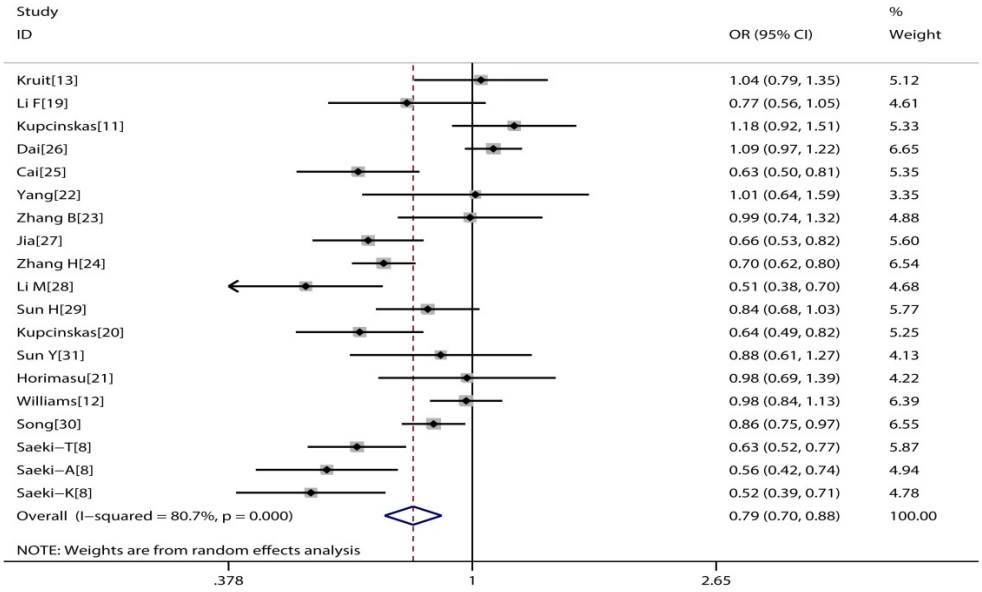

Figure 2. Forest plot of cancer risk associated with MUC1 rs4072037 for allelic genetic model (G *vs.* A).

Table 2. Main results of meta-analysis

Comparisons	Heterogeneity test			Summary OR (95% CI)	Hypothesis test		Datasets
	Q	*P*	I^2(%)		*Z*	*P*	
G vs A	93.38	0	80.7	0.79(0.71,0.89)	4.07	0	19
AG vs AA	84.59	0	78.7	0.72(0.62,0.82)	4.65	0	19
GG vs AA	35.33	0.009	49.1	0.78(0.69,0.88)	4.02	0	19
AG+GG vs AA	94.37	0	80.9	0.72(0.63,0.83)	4.5	0	19
GG vs AG+AA	21.54	0.253	16.4	0.90(0.81,1.01)	1.81	0.07	19

Sensitivity analysis

To reflect the effect of single study on the pooled ORs, we conducted sensitivity analysis by excising each study. Because the corresponding pooled ORs did not materially altered, the meta results were statistically robust (**Figure 6**).

Publication bias

To determine the publication bias of studies, Begg's funnel plot and Egger's test were implemented. The results showed that the figure of the funnel was meristic under the dominant model **(Figure 7)**. In addition, the results of Egger's test quantitatively convinced there was no publication bias in these studies (**Table 4**).

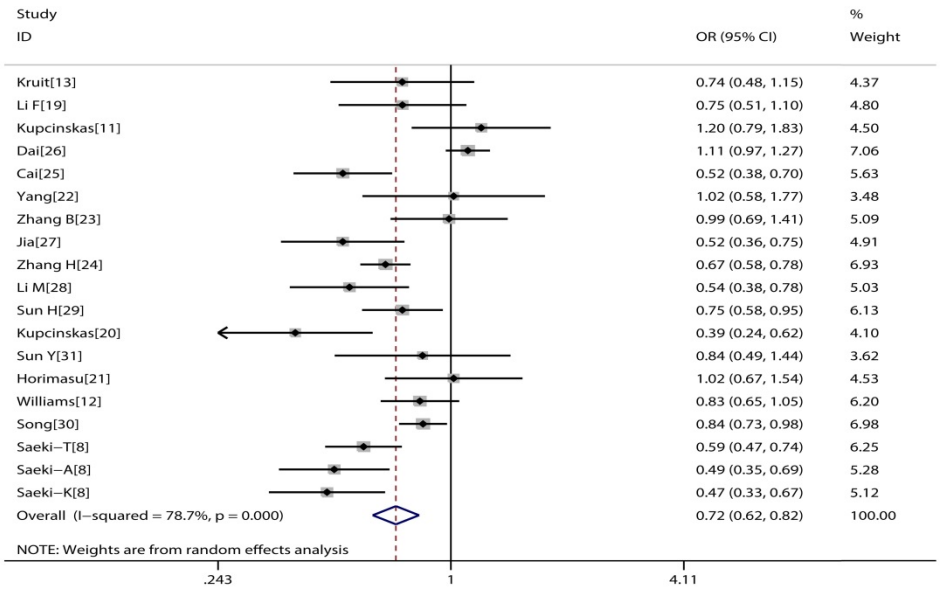

Figure 3. Forest plot of cancer risk associated with MUC1 rs4072037 for heterozygote genetic model (GA *vs.* AA).

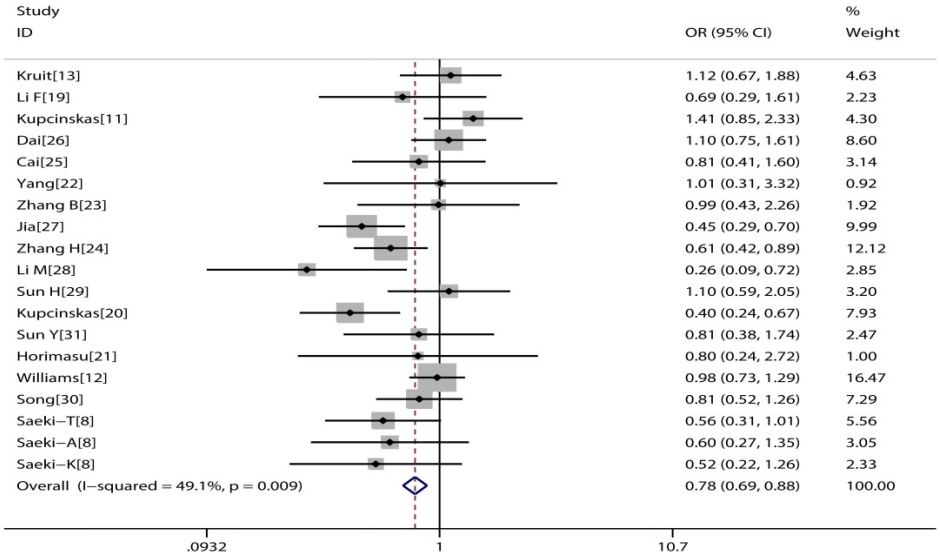

Figure 4. Forest plot of cancer risk associated with MUC1 rs4072037 for homozygote genetic model (GG *vs.* AA)

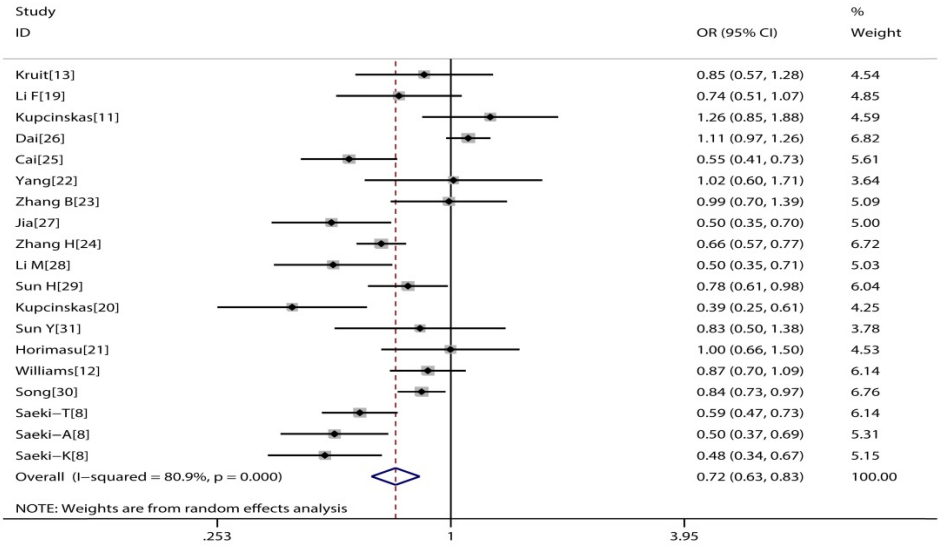

Figure 5. Forest plot of cancer risk associated with MUC1 rs4072037 for dominant genetic model (GG+AG *vs.* AA)

Table 3. Subgroup analysis of meta-analysis

Comparisons	Heterogeneity test			Summary OR (95% CI)	Hypothesis test		Datasets
	Q	*P*	I²(%)		Z	*P*	
Ethnic							
Asian							
G vs A	68.54	0	82.5	0.75(0.65,0.87)	3.92	0	13
AG vs AA	67.31	0	82.2	0.72(0.61,0.85)	3.9	0	13
GG vs AA	13.41	0.34	10.5	0.75(0.64,0.89)	3.31	0.001	13
AG+GG vs AA	71.96	0	83.3	0.72(0.61,0.85)	3.94	0	13
GG vs AG+AA	9.72	0.64	0	0.81(0.69,0.96)	2.48	0.013	13
Caucasian							
G vs A	18.78	0.001	78.7	0.85(0.66,1.10)	1.24	0.215	5
AG vs AA	15.24	0.004	73.7	0.68(0.47,1.01)	1.92	0.054	5
GG vs AA	18.95	0.001	78.9	0.74(0.44,1.24)	1.14	0.255	5
AG+GG vs AA	20	0.001	80	0.70(0.47,1.07)	1.65	0.098	5
GG vs AG+AA	8	0.091	50	0.92(0.76,1.12)	0.82	0.412	5
Cancer type							
Gastric cancer							
G vs A	33.71	0.001	64.4	0.70(0.63,0.78)	6.39	0	13
AG vs AA	37.33	0	67.9	0.64(0.55,0.74)	6.19	0	13
GG vs AA	15.47	0.217	22.4	0.62(0.53,0.73)	5.76	0	13
AG+GG vs AA	41.29	0	70.9	0.64(0.55,0.73)	6.2	0	13
GG vs AG+AA	7.81	0.8	0	0.75(0.64,0.87)	3.68	0	13
Colorectal cancer							
G vs A	4.39	0.036	77.2	0.97(0.63,1.47)	0.17	0.867	2
AG vs AA	2.67	0.102	62.6	0.94(0.59,1.50)	0.26	0.794	2
GG vs AA	2.02	0.155	50.6	1.07(0.54,2.12)	0.19	0.846	2
AG+GG vs AA	3.74	0.053	73.2	0.96(0.57,1.62)	0.16	0.874	2
GG vs AG+AA	1.12	0.29	10.8	1.12(0.77,1.63)	0.61	0.542	2
Other cancers							
G vs A	1.46	0.691	0	1.04(0.96,1.13)	0.91	0.364	4
AG vs AA	6.37	0.095	52.9	0.95(0.78,1.16)	0.53	0.599	4
GG vs AA	0.51	0.917	0	1.03(0.84,1.26)	0.24	0.809	4
AG+GG vs AA	4.13	0.248	27.3	1.03(0.92,1.14)	0.48	0.631	4
GG vs AG+AA	0.97	0.808	0	1.12(0.93,1.34)	1.18	0.24	4
Country							
China							
G vs A	44.47	0	84.3	0.80(0.66,0.96)	2.34	0.019	8
AG vs AA	42.9	0	83.5	0.76(0.61,0.95)	2.38	0.018	8
GG vs AA	10.93	0.142	36	0.80(0.65,0.98)	2.14	0.032	8
AG+GG vs AA	46.14	0	84.8	0.76(0.61,0.95)	2.38	0.018	8
GG vs AG+AA	8.27	0.31	15.3	0.85(0.69,1.04)	1.57	0.117	8
Japan							
G vs A	6.29	0.043	68.2	0.68(0.52,0.91)	2.66	0.008	3
AG vs AA	7.4	0.025	73	0.65(0.45,0.93)	2.37	0.018	3
GG vs AA	0.26	0.877	0	0.60(0.39,0.94)	2.26	0.024	3
AG+GG vs AA	7.14	0.028	72	0.65(0.46,0.91)	2.53	0.011	3
GG vs AG+AA	0.1	0.95	0	0.68(0.44,1.06)	1.72	0.085	3
Other countries							
G vs A	32.41	0	78.4	0.82(0.70,0.97)	2.29	0.022	8
AG vs AA	26.11	0	73.2	0.70(0.56,0.87)	3.15	0.002	8
GG vs AA	22.63	0.002	69.1	0.76(0.56,1.04)	1.69	0.091	8
AG+GG vs AA	31.78	0	78	0.71(0.56,0.90)	2.86	0.004	8
GG vs AG+AA	10.66	0.154	34.3	0.96(0.83,1.10)	0.59	0.552	8
Genotyping method							
TaqMan							
G vs A	82	0	84.1	0.79(0.69,0.91)	3.37	0.001	14
AG vs AA	70.34	0	81.5	0.72(0.61,0.85)	3.97	0	14
GG vs AA	28.35	0.008	54.1	0.78(0.63,0.97)	2.27	0.023	14
AG+GG vs AA	79.16	0	83.6	0.73(0.62,0.86)	3.8	0	14
GG vs AG+AA	18.87	0.127	31.1	0.93(0.82,1.05)	1.19	0.233	14
Other methods							
G vs A	8.4	0.078	52.4	0.77(0.64,0.93)	2.73	0.006	5
AG vs AA	11.64	0.02	65.6	0.71(0.53,0.95)	2.34	0.019	5
GG vs AA	4.47	0.346	10.5	0.63(0.46,0.85)	3.04	0.002	5
AG+GG vs AA	12.33	0.015	67.6	0.71(0.53,0.94)	2.38	0.017	5
GG vs AG+AA	1.32	0.857	0	0.78(0.59,1.03)	1.77	0.077	5
Sample size							
<1000							
G vs A	42.21	0	73.9	0.78(0.66,0.92)	2.92	0.004	12
AG vs AA	34.14	0	67.8	0.70(0.57,0.85)	3.48	0.001	12
GG vs AA	24.33	0.011	54.8	0.71(0.52,0.96)	2.23	0.026	12
AG+GG vs AA	39.97	0	72.5	0.70(0.57,0.87)	3.29	0.001	12
GG vs AG+AA	13.57	0.258	18.9	0.87(0.74,1.03)	1.61	0.107	12
≥1000							
G vs A	47.49	0	87.4	0.80(0.68,0.95)	2.62	0.009	7
AG vs AA	43.27	0	86.1	0.75(0.61,0.91)	2.93	0.003	7
GG vs AA	8.96	0.176	33.1	0.84(0.72,0.99)	2.14	0.032	7
AG+GG vs AA	46.84	0	87.2	0.76(0.62,0.92)	2.83	0.005	7
GG vs AG+AA	7.72	0.26	22.2	0.93(0.80,1.08)	0.99	0.323	7

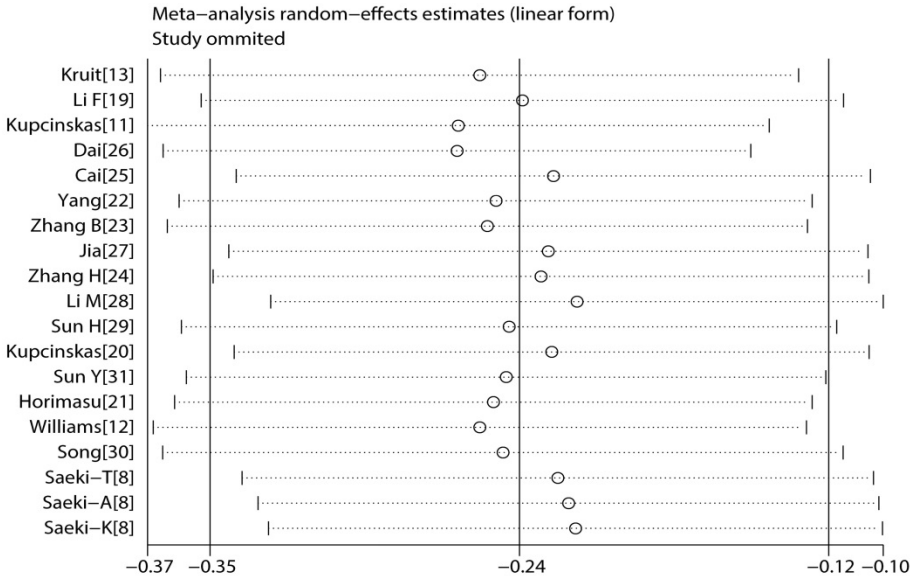

Figure 6. Result of sensitivity analysis.

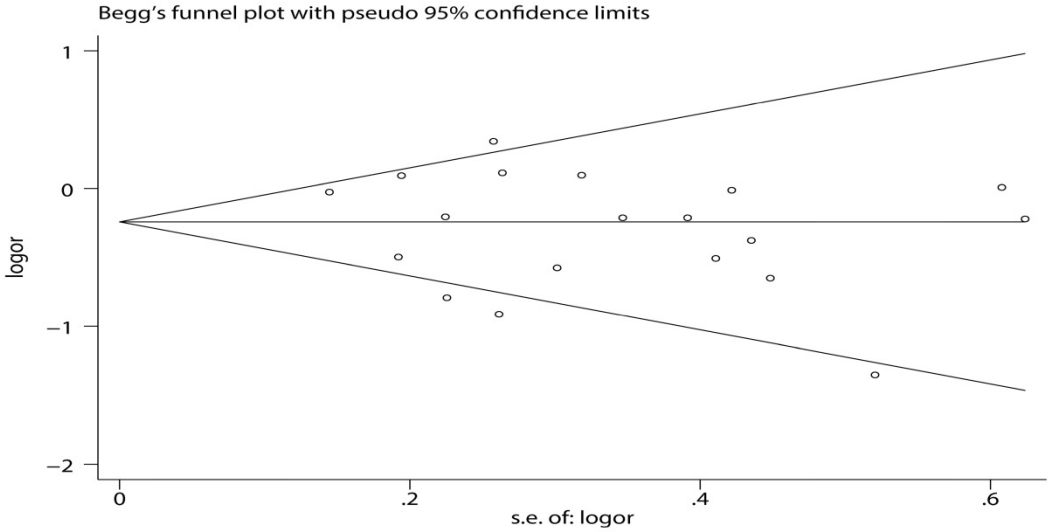

Figure 7. Begg's funnel plot of MUC1 rs4072037 polymorphism and cancer risk for homozygous genetic model (GG *vs*. AA)

Table 4. Publication bias of meta-analysis for Egger's test

Model	T-value	*P*-value	95% CI of intercept value
G vs A	-1.33	0.202	(-4.614735,1.053355)
AG vs AA	-1.63	0.121	(-4.139911,0.5275983)
GG vs AA	-0.97	0.345	(-2.638502,0.9741915)
AG+GG vs AA	-1.47	0.159	(-4.310014,0.7678419)
GG vs AG+AA	-1.52	0.147	(-2.141581,0.3494686)

Table 5. The main result of removing Song et al and Zhang B et al.

Comparisons	Heterogeneity test			Summary OR (95% CI)	Hypothesis test		Datasets
	Q	*P*	I^2(%)		*Z*	*P*	
G vs A	18.04	0.054	44.6	0.67(0.63,0.72)	11.37	0	11
AG vs AA	18.31	0.05	45.4	0.61(0.56,0.66)	11.29	0	11
GG vs AA	12.28	0.267	18.6	0.58(0.48,0.69)	5.91	0	11
AG+GG vs AA	21.05	0.021	52.5	0.59(0.52,0.67)	7.81	0	11
GG vs AG+AA	7.03	0.723	0	0.73(0.62,0.86)	3.69	0	11

Discussion

Meta-analysis is a crucial statistical technique which has more statistical power than a single study. It can quantitatively combine analyses from different studies. Because of the association between cancer risk and MUC1 rs4072037 polymorphism are conflicted, we performed this meta-analysis to solve the problem. In our meta-analysis, we found the G allele locus on rs4072037 was associated with significantly decreased cancer risk. Subgroup analysis by cancer type indicated that G allele was associated with decreased gastric cancer risk, but not colorectal cancer or other cancers (breast cancer, lung cancer, ovarian cancer and esophagus cancer). We performed subgroup analysis by ethnicity and found G allele was associated with decreased cancer risk among Asian but not Caucasian. The consequences was not changed when stratification by country, genotyping methods or sample size. The MUC1 gene is used to encode membrane-bound glycosylated phosphor-protein and it is a member of the mucin family. There were several studies focus on the relationship between MUC1 rs4072037 polymorphism and the risk of cancer. However, Zheng et al. [32] Giraldi et al.[33] and Liu et al. [34] included fewer studies and only focused on the relationship of the gastric cancer and MUC1 rs4072037 polymorphism. Duan et al.[35] covered only 3 types of cancer, including 8 researches on cancer of stomach and one each on breast cancer and colorectal cancer. Comparing with these meta-analyses, our meta-analysis has involved more studies, which 12551 cases and 13436 controls were involved. In addition, the result of Duan et al showed MUC1 rs4072037 polymorphism was associated with decreased cancer risk in recessive model, but the result of our meta-analysis showed they have no association (OR=0.90, 95%CI: 0.81-1.01, *P*=0.07). In the subgroup analysis, Duan et al found a decreased association between MUC1 rs4072037 polymorphism and cancer risk in allelic model, heterozygote model and dominant model among Caucasian. However, the result of our meta-analysis showed they have no association among Caucasian under all genetic model.

When we interpreted the results of meta-analyses, there was possibly heterogeneity. It is an important goal to discover the provenience of heterogeneity in meta-analysis [36]. To assess the heterogeneity, the I^2 statistic was used. We found the results of our meta-analysis showed significant heterogeneity in allelic, co-dominant and dominant models. To discover the provenience of heterogeneity, we performed subgroup analysis, meta regression and sensitivity analysis. In the subgroup analysis, we discovered type of cancer may be a source of heterogeneity. Then we conducted sensitivity analysis in GC group. When we took out the Song et al [30]

and Zhang B et al [23], the I^2 statistic was significantly decreased (**Table 5**).

There were still some limits in our meta-analysis. Firstly, publication bias might exist because we just included published studies. Secondly, we knew diet, smoking and other environmental risk might be factors for cancer. However, because of limited information, we cannot explore the associations between these factors and cancers. Last but not least, the heterogeneity of our meta-analysis in some models is high. Though we found the source of heterogeneity, we thought there might be others.

In summary, our meta-analysis found MUC1 rs4072037 polymorphism was associated with lower cancer risk, particularly in gastric cancer and Asians. It might be used as a tumor marker.

Competing Interests

The authors have declared that no competing interest exists.

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