RESEARCH ARTICLE

PLCE1 rs2274223 Polymorphism and Susceptibility to Esophageal Cancer: a Meta-analysis

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Abstract

Purpose: To investigate and study the relationship between the PLCE1 rs2274223 gene polymorphism and susceptibility to esophageal cancer by meta-analysis. Materials and Methods: The literature was searched in Wanfang, CNKI, PubMed, CBM, Web of Science, MEDLINE, EMBASE, Springer, Elsevier and Cochrane databases from the date of January 1st 2004 to April 1st 2014 to collect case-control studies on the PLCE1 polymorphism and susceptibility to esophageal cancer. For the population genotype distributions of both esophagus cancer and control groups, their odds ratios (ORs) and 95% confidence intervals (CIs) were taken as effect indexes. Disqualified studies were excluded. Odds ratios of PLCE1 rs2274223 genotype distributions in the group of patients with esophageal cancer and the group of healthy control were calculated. The meta-analysis software, RevMan5.0, was applied for heterogeneity test, pooled OR and 95% confidence intervals. Sensitivity analysis and publication bias were also explored. Results: A total of twelve case-control studies were included, covering a total of 9, 912 esophageal cancer cases and 13, 023 controls were included. The pooled odds ratio of PLCE1 rs2274223 genotype GA *vs* AA was 1.29 (95%CI=1.17~1.43), *p*<0.01, GG *vs* AA was 1.65 (95%CI=1.32~2.05), *p*<0.01, GG/GA *vs* AA was 1.30 (95%CI=1.16~1.46), *p*<0.01 and GG *vs* GA/AA was 1.48 (95%CI=1.22~1.80), *p*<0.01. The PLCE1 rs2274223 polymorphism was thus associated with risk of esophageal cancer in all genetic models. In the stratified analysis by ethnicity, and source of controls, no significantly increased risk was observed for white persons. There was no obvious publication bias detected. Conclusions: This meta-analysis showed there was a significantly association between PLCE1 rs2274223 polymorphism and esophageal cancer in yellow race populations. Due to some minor limitations, our findings should be confirmed in further studies.

Keywords: Esophageal cancer - PLCE1 rs2274223 - gene polymorphism - meta-analysis - case-control study

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Introduction

Esophageal carcinoma (EC) is one of the most common cancers worldwide and ranks as the sixth cause of cancer-related death. It has been estimated that there were nearly 400 thousand new diagnosed cases worldwide per year (Han et al., 2012). It has been suggested that Esophageal carcinoma is a combined effect of multiple factors, which contains both environmental factors and genetic defects. Phospholipase C epsilon1 (PLCE1) may regulate cell growth, The PLCE1 gene is a unique member of the phospholipase family. PLCE1 encodes the phospholipase C epsilon 1 (PLCe1) that catalyses the hydrolysis of phosphatidylinositol-4, 5-bisphosphate into the secondary messengers inositol 1, 4, 5-trisphosphate and diacylglycerol (DAG), which participate in cell growth, differentiation and gene expression. Recent studies have reported that PLCE1 plays crucial roles in carcinogenesis (Zhao et al., 2014) and progression of several types of cancer, and it has been a hot topic to investigate and study the relationship between PLCE1 rs2274223 polymorphism and susceptibility to esophageal cancer (Yu et al., 2013). Numerous case-control studies and cohort studies on the association of PLCE1 rs2274223 polymorphisms with esophageal cancer susceptibility have been conducted. However, the association PLCE1 rs2274223 polymorphism and esophageal cancer risk has not been elucidated. Therefore, a system review and meta-analysis was performed. Recent studies indicated that rs2274223 was associated with an increased risk of esophageal cancer. Interestingly, another study proved that rs2274223 was associated with a protective effect against esophageal cancer. To date, the association between the rs2274223 polymorphism and the susceptibility of esophageal cancer are inconclusive, partially because of the different effects of the polymorphism on variants of esophageal cancer risk and the relatively small sample size in each of published studies. At home and abroad, there is

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no special quantitative comprehensive study on esophageal carcinoma and PLCE1 rs2274223 gene polymorphism. Therefore, we performed a meta-analysis on these eligible studies to investigate the precise relationship PLCE1 rs2274223 polymorphism and susceptibility to esophageal cancer, which would have a much greater possibility of reaching reasonably strong conclusions.

Materials and Methods

Identification and eligibility of relevant studies

Wanfang, CNKI, PubMed, CBM, Web of Science, MEDLINE, EMBASE, Springer, Elsevier and Cochrane databases were carried out to find relevant papers using the following search equation (PLCE1 or phospholipase Cε1 or PLCE1 rs2274223 or phospholipase or phospholipase C epsilon 1) and (genetic polymorphism or susceptibility or carcinoma of the head and neck or SCCHN) and (esophageal cancer or esophagus or esophageal neoplasm or digestive tract cancer or carcinoma of the esophagus or esophageal carcinoma). The selection was done without restriction on language, but they only included published articles written in English or Chinese. We used the PubMed option ''Related Articles'' for each study to get additional potentially relevant articles. Reference lists were checked and researchers were contacted for additional literatures.

Selection criteria

Studies were selected if they met the following criteria: (1) the study investigated the association between PLCE1 rs2274223 polymorphism and the risk of esophageal cancer, (2) association study with a case-control design, (3) contained available genotype frequency or data sufficient to compute these values, (4) odds ratios (ORs) or available data for their calculation were reported, (5) genotype distribution in the control population consistent with HWE, (6)genotypes must be confirmed through Molecular biological technology. Relevant articles published were from January 1st 2004 to April 1st 2014. Studies excluded if conference abstracts, narrative reviews.

Data extraction and quality assessment

According to pre-established selection criteria, relevant data were systematically extracted by observer using a standardized form. The researcher collected the following data: the first author, year of publication, ethnicity of the study population, cancer type, the genotypes frequencies of the PLCE1 rs2274223 polymorphism between patients and controls, language of publication, source of country, design of study, sample size, source of control, genotyping method, evidence of HWE, etc.

The quality of studies was assessed according to the Strengthening the Reporting of Genetic Association Studies (STREGA) criteria (Little et al., 2009), and studies according with STREGA criteria were defined as high-quality studies.

Statistical analysis

Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were employed to estimate the strength of association between the PLCE1 rs2274223 polymorphisms and esophageal cancer susceptibility. Heterogeneity among the studies included in the meta analysis was evaluated by the chi-square based Q test and quantified by the I^2 metric. When no statistical heterogeneity was found (I^2<40% or $P(Q)$>0.10), the ORs and 95%CI would be estimated for each study in the fixed-effect model. Otherwise, the random-effect model was applied (Ding et al., 2011; Pan et al., 2013; Wei et al., 2013; Wang et al., 2013). Statistical tests were performed using the program Review Manager5.0 software. We also performed subgroup analysis to investigate potential sources of heterogeneity. The funnel plot was drawn to evaluate publication bias and the unsafe coefficient were also done to check the publication bias. Sensitivity analysis was carried out by sequential omission of individual studies. The Hardy-Weinberg equilibrium (HWE) in the controls was evaluated in our meta analysis and p<0.05 was considered representative of a departure from HWE. All statistical tests were two-sided. The recessive genetic model, dominant genetic model and additive genetic models were used to calculate the pooled ORs and 95%CIs for performed by ethnic group and source of controls. In addition, allelic G was assumed to be a risk factor of esophageal cancer.

Results

The flow diagram illustrates the main reasons for studies searching and selecting (Figure 1), and the selected study characteristics were summarized in Table 1. A total of 12 eligible publications (Bye et al., 2012; Dura et al., 2012; Gu et al., 2012; Hu et al., 2012; Palmer et al., 2012; Song et al., 2012; Zhou 2012 (unpublished); Chen et al., 2013; Cui et al., 2013; Duan et al., 2013; Piao et al., 2013; Wang et al., 2013) concerning the PLCE1 rs2274223 polymorphisms and 9912 cases and 13023 controls were included in the meta-analysis. The genotype distribution of the controls in all the studies was consistent with Hardy-Weinberg equilibrium. Among the 12 studies, there were 6 studies of population-based population and 6 studies of hospital-based population. The 12 studies included 9 studies of yellow race, 2 studies of white race and 1study of black race. Among the 12 studies, there were 10 studies of English and 2 Chinese.

Quantitative synthesis

The evaluation of the association between the

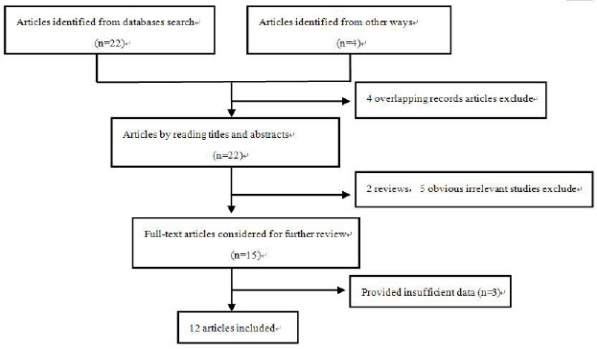

Figure 1. Flow Diagram Summarizing the Search Strategy

PLCE1rs2274223 polymorphism and the susceptibility to esophageal cancer is presented in Table 2 and Figure 2. Heterozygote comparison, GA *vs* AA, GG *vs* AA, GG/GA *vs* AA and GG *vs* GA/AA have high probabilities of statistical heterogeneity (*P value* =0.05, 0.003, 0.002 and 0.01 respectively, I^2=47%, 64%, 68% and 58% respectively). So the random-effect model was applied. Overall, the variant G allele of rs2274223 could increase the risk of esophageal cancer in all genetic models (GA *vs* AA: OR=1.29, 95%CI=1.17~1.43, p<0.01; GG *vs* AA:OR=1.65, 95%CI=1.32~2.05, p<0.01; GG/GA *vs* AA:OR=1.30, 95%CI=1.16~1.46, p<0.01, GG *vs* GA / AA:OR=1.48, 95%CI=1.22~1.80, p<0.01).

Additionally, in the analysis stratified by source of control (Table 2 and Figure 3), the PLCE1 rs2274223 polymorphism was not linked to a higher risk for esophageal cancer in GG/GA *vs* AA of the studies based on population, but it was linked to a higher risk for esophageal cancer in other models, their OR and 95%CI: GA *vs* AA: 1.21 (1.08, 1.35), GG *vs* AA: 1.40 (1.14, 1.73), and GG *vs* GA/AA: 1.31 (1.06, 1.60), respectively. However, the PLCE1 rs2274223 polymorphism was linked to a higher risk for esophageal cancer in the studies based on hospital. OR and 95%CI: GA *vs* AA: 1.38 (1.29, 1.48), GG *vs* AA:1.98 (1.38, 2.84), GG/GA *vs* AA:1.47 (1.29, 1.67) and GG *vs* GA/AA:1.71 (1.22, 2.38), respectively. In the analysis stratified by ethnicity, the PLCE1 rs2274223 polymorphism was significant linked to a higher risk for esophageal cancer in the studies based on yellow race, their OR and 95%CI: GA *vs* AA:1.38 (1.30, 1.47), GG *vs* AA: 1.92 (1.60, 2.29), GG/GA *vs* AA: 1.39 (1.24, 1.57) and GG *vs* GA/AA:1.68 (1.46, 1.94) respectively; But the PLCE1 rs2274223 polymorphism was not linked to a higher risk for esophageal cancer in the studies based on white race, their OR and 95%CI: GA *vs* AA: 0.93 (0.64, 1.35), GG *vs* AA: 1.02 (0.68, 1.54), GG/GA *vs* AA: 0.96 (0.74, 1.26) and GG *vs* GA/AA: 1.04 (0.71, 1.54), respectively.

Analysis of source of heterogeneity

When evaluating the association between the PLCE1 rs2274223 polymorphism and the susceptibility to esophageal cancer, we found that there was significant heterogeneity. Thus, we assessed the source of heterogeneity for the dominant model comparison by examining ethnicity, source of controls, genotyping method and year. Subgroup analysis showed that none of these concomitant variables could account for the

Table 1. Characteristics of Literatures Included in the Meta-analysis

Author	year	country	Ethnicity	Source of controls	Cancer type	Genotyping method	Cases			Controls			HWE
							AA	GA	GG	AA	GA	GG	
Bye	2012	South African	Black race	Hospital	EC	TaqMAN	218	338	116	612	819	276	0.943
Chen	2013	China	Yellow race	Hospital	EC	MALDI-TOFMS	97	84	19	178	111	11	0.211
Cui	2013	China	Yellow race	Hospital	EC	MALDI-TOFMS	108	193*		114	133*		-
Duan	2013	China	Yellow race	Hospital	EC	PCR-LDR	193	150	38	281	123	16	0.582
Dura	2012	Netherlands	White race	Population	EC	RT-PCR	160	154	30	279	247	54	0.95
Gu	2012	China	Yellow race	Hospital	EC	MALDI-TOFMS	202	147	30	233	119	19	0.457
Hu	2012	China	Yellow race	Population	EC	TaqMAN	594	400	67	754	399	58	0.577
Palmer	2012	America	White race	Population	EC	TaqMAN	74	68	17	86	107	17	0.187
Piao	2013	South Korea	Yellow race	population	EC	RT-PCR	153	140	29	909	684	107	0.148
Song	2012	China	Yellow race	Hospital	EC	Sequenom	2713	2172	449	3133	1795	263	0.776
Wang	2013	China	Yellow race	Population	EC	RT-PCR	147	95*		323	253*		-
Zhou	2012	China	Yellow race	Population	EC	PCR-LDR	248	227	42	291	191	28	0.646

*Is represent for sum of people with genotype GA and GG; EC, esophageal cancer; HWE, Hardy–Weinberg equilibrium

Table 2. Stratified Analyses of the PLCE1 rs2274223 Polymorphism on Esophageal Cancer Risk

Variables		Total	Race		Control source	
			Yellow	White	Population	Hospital
Number of comparisons		12	9	2	6	6
case/control		9912/13023	8737/10526	503/790	2645/4787	7267/8236
GA vs AA	OR	1.29 (1.17, 1.43)	1.38 (1.30, 1.47)	0.93 (0.64, 1.35)	1.21 (1.08, 1.35)	1.38 (1.29, 1.48)
	P (z)	<0.01	<0.01	0.7	<0.01	<0.01
	P (Q)	0.05	0.59	0.14	0.14	0.22
	I^2 (%)	47	0	53	43	31
GG vs AA	OR	1.65 (1.32, 2.05)	1.92 (1.60, 2.29)	1.02 (0.68, 1.54)	1.40 (1.14, 1.73)	1.98 (1.38, 2.84)
	P (z)	<0.01	<0.01	0.91	<0.01	<0.01
	P (Q)	0.003	0.24	0.69	0.45	0.002
	I^2 (%)	64	25	0	0	77
GG/GA vs AA	OR	1.30 (1.16, 1.46)	1.39 (1.24, 1.57)	0.96 (0.74, 1.26)	1.13 (0.95, 1.34)	1.47 (1.29, 1.67)
	P (z)	<0.01	<0.01	0.79	0.16	<0.01
	P (Q)	0.0003	0.009	0.25	0.02	0.08
	I^2 (%)	68	61	25	63	50%
GG vs GA/AA	OR	1.48 (1.22, 1.80)	1.68 (1.46, 1.94)	1.04 (0.71, 1.54)	1.31 (1.06, 1.60)	1.71 (1.22, 2.38)
	P (z)	<0.01	<0.01	0.83	0.01	0.002
	P (Q)	0.01	0.37	0.38	0.61	0.003
	I^2 (%)	58	8	0	0	76

substantial heterogeneity observed (Table 1).

Sensitivity analysis

Sensitivity analysis was performed to assess the influence of each individual study on the pooled OR by sequential removal of individual studies. But the corresponding pooled ORs were not altered materially e.g. Bye, 2012; Palmer, 2012; Dura, 2012; Gu, 2012; Hu, 2012; Wang, 2013; Zhou, 2012; Song, 2012; Chen, 2013; Cui, 2013; Duan, 2013 and Piao, 2013 sequential were removal: GG/GA *vs* AA, OR (95%CI) and *p* value was: 1.32 (1.16, 1.49), $p<0.05$; 1.34 (1.19, 1.49), $p<0.05$; 1.32 (1.17, 1.49), $p<0.05$; 1.29 (1.13.1.46), $p<0.05$; 1.30 (1.14, 1.48), $p<0.05$; 1.35 (1.21, 1.50), $p<0.05$; 1.29 (1.13, 1.46), $p<0.05$; 1.28 (1.11, 1.46), $p<0.05$; 1.29 (1.14, 1.45), $p<0.05$; 1.29 (1.14, 1.46), $p<0.05$; 1.26 (1.12, 1.41), $p<0.05$; and 1.30 (1.15, 1.48), $P<0.05$, suggesting that our results were statistically robust.

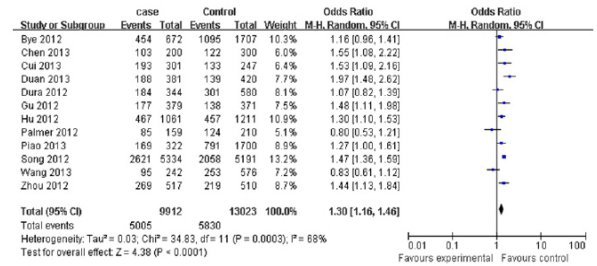

Figure 2. Forest Plot from the Meta-Analysis of PLCE1 rs2274223 Polymorphism ("GG/GA *vs* AA") and the Risk of Esophageal Cancer using Dominant Genetic Model

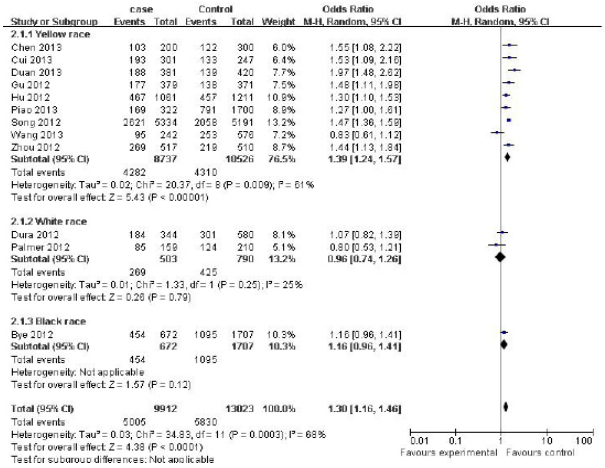

Figure 3. Forest Plot from the Meta-Analysis of PLCE1 rs2274223 Polymorphism ("GG/GA *vs* AA") and the Risk of Esophageal Cancer Stratified by Ethnicity Using Dominant Genetic Model

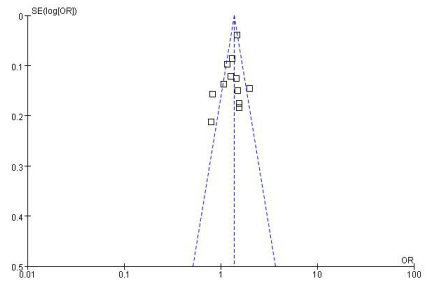

Figure 4. Funnel Plots Under the Dominant Genetic Model to Identify the Publication Bias

Publication bias

The funnel plot and the unsafe coefficient were performed to assess the publication bias of the literature. The shape of the funnel plots did not reveal any evidence of obvious asymmetry (Figure 4 shows the funnel plot of the overall GG/GA *vs* AA comparison). Then, the unsafe coefficient was used to provide statistical evidence of funnel plot symmetry. Results still did not show any obvious evidence of publication bias ($N_{fs0.05}$=421 and $N_{fs0.01}$=202).

Discussion

The relationship between PLCE1 rs2274223 gene polymorphism and susceptibility to esophageal cancer has caused wide public concern over the recent years. Several studies have shown that relevant genetic loci were rs2274223, rs11187870, rs753724, rs3765524, rs3781264 and rs11187842 and so on. The rs2274223 locates in the 26 exon and causes histidine transfer to arginine (Ma et al., 2011; Zhou et al., 2011; Yu et al., 2013). It has been a hot topic to study the relationship between PLCE1 rs2274223 gene polymorphism and susceptibility to head and neck cancer and the relationship between PLCE1 rs2274223 gene polymorphism and susceptibility to esophageal cancer has caused wide public concern (Gbadegesin et al., 2009; Ma et al., 2011; Abnut et al., 2012; Mai et al., 2012; Cui et al., 2014).

In the current meta-analysis, we ascertained that the PLCE1 rs2274223 polymorphism was significantly associated with increased esophageal cancer risk. To our knowledge, this is the first study to specially investigate the association between the PLCE1 rs2274223 polymorphism and the risk of esophageal cancer across different ancestries.

Most literatures reported the strong association of the susceptibility locus rs2274223 with the increased risk of esophageal cancer, however, it was unlikely that the PLCE1 rs2274223 SNP played a role in esophageal cancer susceptibility. Although many epidemiological studies regarding the PLCE1 rs2274223 polymorphism on the risk of variants of esophageal cancer had been conducted, the results were conflicting and inconclusive because of various reasons, such as different ethnicities, resident countries, sample size, environmental factors, diet habits and genotyping method. To provide a more comprehensive analysis on the association, we carried out this meta-analysis based on 12 case control studies with 9912 cases and 13023 controls and indicated that the PLCE1 rs2274223 polymorphism was associated with increased risk of esophageal cancer.

In the analysis stratified by ethnicity, we observed increased susceptibility to esophageal cancer in the four genetic models, except for 2 studies about esophageal cancer in white race. Although the exact mechanism for these ethnic differences is still unknown, one possible reason is due to differences in genetic backgrounds and in the environmental and lifestyle context. Esophageal cancer

is the result of diverse gene-environment interactions (Wu et al., 2006; Tang et al., 2011; Wang et al., 2011; Zhao et al., 2011; Zhao et al., 2012; Yang et al., 2013). In addition, because of the gene-gene interaction, the influence of the PLCE1rs2274223 polymorphism might be masked by the presence of other genes which were unidentified yet in the development of cancer. Other factors such as selection bias, different selection criteria and limited number of studies with available data may have insufficient statistical power to detect a difference and may also generate a fluctuated risk estimate.

Some limitations of this meta-analysis may have affected the objectivity of the conclusions and should be considered in interpreting the results. Firstly, the quantity of selected studies was not sufficiently large for a comprehensive analysis, and these studies include yellow race, white race and black race, however, only a study is about black race; Secondly, we only focused on the PLCE1 rs2274223 polymorphism, and did not cover the other polymorphisms of genetic locus. It is possible that the potential role of the examined polymorphism is diluted or masked by other gene-gene or gene-environment interactions; Thirdly, potential published bias cannot be completely ruled out, because we only retrieved studies published articles. Fourthly, because of limitation in language, we only retrieved studies from English and Chinese journals; Fifthly, esophageal cancer is the result of diverse gene-environment interactions, we could not retrieve more detailed individual data which were available, such as occupation, histological types and so on; Sixthly, there are two Chinese literatures among these selected literatures. Overall, in spite of these limitations, our present meta-analysis also had some advantages. Firstly, we estimated the association conclusively between the PLCE1 rs2274223 polymorphism and esophageal cancer susceptibility, and further showed the significant association especially among Asians rather than Europeans; Secondly, funnel plot and unsafe coefficient were used to test the publication bias of the included studies. Both the shape of funnel plot and unsafe coefficient's results show no obvious publication bias; Thirdly, we pooled a substantial number of cases and controls from different studies and avoid limitation of resident location, which greatly increased the statistical power of the analysis. This suggests that the publication bias have little effect on the results in our study and the results of our meta-analysis are relatively stable.

In conclusion, our meta-analysis suggests that the PLCE1 rs2274223 polymorphism was obviously associated with esophageal cancer susceptibility, however, the PLCE1 rs2274223 polymorphism was not linked to susceptibility of esophageal cancer in the studies based on white race. There were relationship between many genetic locus polymorphism with esophageal cancer susceptibility (Peng et al., 2004; Wu et al., 2006; Zhao et al., 2011; Wang et al., 2011; Tang et al., 2011; Zhao et al., 2012; Yang et al., 2013).

This meta analysis only addressed the association of PLCE1 rs2274223 polymorphism with esophageal cancer susceptibility, however, we believe that further studies assessing the effect of gene-gene or gene-environment interactions may eventually achieve a more comprehensive understanding. This meta-analysis provides an anchoring point for better understanding of the pathogenesis of esophageal cancers and a more sufficient and reliable evidence.

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