

RESEARCH ARTICLE

Prognostic Value of PLCE1 Expression in Upper Gastrointestinal Cancer: a Systematic Review and Meta-analysis

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Abstract

Background: A number of studies have identified a shared susceptibility locus in phospholipase C epsilon 1 (PLCE1) for esophageal squamous cell carcinoma (ESCC) and gastric cardia adenocarcinomas (GCA). However, the results of PLCE1 expression in esophageal and gastric cancer remain inconsistent and controversial. Moreover, the effects on clinicopathological features remain undetermined. This study aimed to provide a precise quantification of the association between PLCE1 expression and the risk of ESCC and GCA through meta-analysis. **Materials and Methods:** Eligible studies were identified from PubMed, Wanfang Data, ISI Web of Science, and the Chinese National Knowledge Infrastructure databases. Using RevMan5.2 software, pooled odds ratios (ORs) with 95% confidence intervals (CIs) were employed to assess the association of PLCE1 expression with clinicopathological features relative to ESCC or GCA. **Results:** Seven articles were identified, including 761 esophageal and gastric cancer cases and 457 controls. Overall, we determined that PLCE1 expression was associated with tumor progression in both esophageal cancers (pooled OR=5.93; 95% CI=3.86 to 9.11) and gastric cancers (pooled OR=9.73; 95% CI=6.46 to 14.7). Moreover, invasion depth (pooled OR=3.62; 95% CI=2.30 to 5.70) and lymph node metastasis (pooled OR=4.21; 95% CI=2.69 to 6.59) were linked with PLCE1 expression in gastric cancer. However, no significant associations were determined between PLCE1 overexpression and the histologic grade, invasion depth, and lymph node metastasis in esophageal cancer. **Conclusions:** Our meta-analysis results indicated that upregulated PLCE1 is significantly associated with an increased risk of tumor progression in ESCC and GCA. Therefore, PLCE1 expression can be appropriately regarded as a promising biomarker for ESCC and GCA patients.

Keywords: PLCE1 - upper gastrointestinal cancer - gastric - esophageal - meta-analysis - expression

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Introduction

Cancer is the leading cause of death in both developed and developing countries. Almost 12.7 million cancer cases and 7.6 million cancer deaths have recently been reported worldwide. Among these cases, gastric and esophageal cancers are the most lethal malignancy and have caused 406,800 and 738,000 deaths, respectively (Jemal et al., 2011). The incidence of these two cancers varies considerably according to geographic locations and ethnicity. Southern and Eastern Africa and Eastern Asia have the highest rates of esophageal cancer (Tran et al., 2005). The main risk factors of esophageal cancer include poor nutritional status, low intake of fruits and vegetables, and consumption of high temperature beverages (Islami et al., 2009a; Wu et al., 2009; Cui et al., 2014a). The highest rates of gastric cancer are found in Eastern Asia, Eastern Europe, and South America (Jemal et al., 2011).

Helicobacter pylori infection is the major etiologic factor for all ethnicities (Mbulaiteye et al., 2009). Furthermore, another influencing factor has been considered in combination with the environment-genetic predisposition.

Three large-scale and independent genome-wide association studies (GWAS) in China recently reported that a new susceptibility locus (rs2274223: A5780G), located in exon 26 of Phospholipase C epsilon 1 (PLCE1) is strongly associated with the risk of esophageal and gastric cancers in Chinese population (Abnet et al., 2010; Wang et al., 2010; C et al., 2011). PLCE1, which is located in chromosome 10q23, encodes a phospholipase that hydrolyzes phosphatidyl-inositol 4,5-bisphosphate to 1,2-diacylglycerol and inositol 1, 4, 5-trisphosphate (Wing et al., 2003). This phospholipase has been reportedly associated with intracellular signaling through the regulation of a variety of proteins, such as the protein kinase C (PKC) isozymes and the proto-oncogene ras

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(Rhee, 2001; Bunney et al., 2009). Also replicated independent studies have validated the association of PLCE1 polymorphism with esophageal cancer in Chinese Kazakh and Kashmiri population (Cui et al., 2013; Malik et al., 2014). Recent studies have shown that, increased PLCE1 expression is related to the development of bladder cancer (Ou et al., 2010). PLCE1 overexpression also has positive effects on the transfer of the squamous cell carcinoma of the head and neck (Ma et al., 2011). However, downregulation of PLCE1 expression has a significant relationship with colorectal cancer according to the study of Wang et al. (2012b). Luo et al. (2014) determined that PLCE1 is a suppressor of P53 in NSCLC, which was inconsistent with the results of Wang. Thereafter, a different pattern of PLCE1 expression is said to exist in different types of cancer, including cancers of the intestine, skin, colon, and rectum (Gonzalez-Garcia et al., 2005; Bourguignon, 2006; Wang et al., 2007; Baertschiger et al., 2009; Ou et al., 2010).

Several recent studies have focused on the association between PLCE1 expression and the risk of esophageal and gastric cancers. However, results of recent studies remain inconsistent in terms of the correlation of PLCE1 expression detected by immunohistochemistry (IHC) and pathological analysis. Several studies have identified PLCE1 overexpression as a susceptibility factor related to the progression of gastric cancer (Ren, 2011; Wu, 2011; Liang, 2012; Zhang et al., 2012) and esophageal cancer (Zhao et al., 2012). However, the result of the study of Wang indicated a low level of PLCE1 in gastric tumor tissues, which may be attributed to the PLCE1 SNP rs2274223 A<G change that reduces gene expression (Wang et al., 2012a). Similarly, Zhu et al. determined that PLCE1 protein overexpression may be an important molecular event in Kazakh esophageal squamous cell carcinoma (ESCC) cases and may be related to the progression and prognosis of Kazakh ESCC (Zhu et al., 2012). This result is in agreement with the findings of Chen (Chen et al., 2013), who determined that PLCE1 overexpression correlates with lymph node metastasis and advanced TNM stages of Kazakh ESCC, implicating PLCE1 in cancer metastasis and aggressiveness in ethnic Kazakh patients with ESCC. However, the opposite result in the study of Hu et al. (2012b) indicated that overall PLCE1 mRNA expression was lower in tumor than in paired normal tissues. Moreover, the comparison of PLCE1 protein levels did not determine any difference between matched normal and tumor tissues. The limited availability of samples may result in variations in the clinical significance of the results.

Thus, we conducted a meta-analysis of these recent articles to identify the statistical evidence of the association between PLCE1 expression and the risk of ESCC and GCA that have been investigated. After assessing all eligible case-control studies involving 761 esophageal and gastric cancer cases and 457 controls, we determined that PLCE1 expression was associated with tumor progression in both esophageal and gastric cancers. Moreover, invasion depth and lymph node metastasis were correlated with PLCE1 expression in gastric cancer.

Materials and Methods

Literature sources and search strategies

A systematic search current to May 10, 2014 was conducted by using PubMed, Wanfang Data, ISI Web of Science, and the Chinese National Knowledge Infrastructure databases. We identified articles using the following strategy: (“PLCE1” or “phospholipase C epsilon-1”) and (“ESCC” or “esophageal cancer”) and (“gastric cancer” and “stomach cancer”). Our study was conducted in accordance with the standard for meta-analysis of observational studies in epidemiology. All eligible studies were retrieved and their references were checked for other relevant studies.

Inclusion and exclusion criteria

The studies were selected on the basis of the following inclusion criteria: (1) case-control studies that evaluated the clinicopathologic correlation of PLCE1 expression in gastric and esophageal cancers, (2) measure of PLCE1 expression in the gastric cancer and esophageal cancer tissue by IHC, (3) studies that are not in English and Chinese were not considered, and (4) studies should have been published in academic journals. Furthermore, the following exclusion criteria were set: (1) failure to provide detailed data, such as those presented in abstracts, meeting reports and reviews; (2) clinical characteristics were not reported; and (3) the studies repeated or overlapped with those in other publications..

Data extraction

All studies included in this meta-analysis met the selection criteria. Two reviewers (Xiaobin Cui and Hao Peng) independently reviewed and extracted data from all eligible studies. The following information was extracted: first author, year, origin, study period, cases, ages and method. After extraction, data were reviewed and compared by the same reviewers. If they had different opinions about the data, then such disagreements would be resolved by consensus among the reviewers.

Meta-analysis

Analysis was performed using Review Manager (version 5.0 for Windows; The Cochrane Collaboration, 2003). The strength of the association between PLCE1 expression and gastric cancer and esophageal cancers was measured by odds ratios (ORs) with 95% confidence intervals (CIs). I^2 statistics was also computed on the basis of the Q statistic by subtracting the degrees of freedom and dividing by the Q statistic value. Given that heterogeneity ($p>0.05$) was absent among the studies, a random effect model would be chosen to pool the ORs; if not, then a fixed effect model was selected.

Results

Study inclusion and characteristics

We identified seven studies for analysis on the basis of the inclusion criteria. A total of 68 abstracts were identified and screened, and 16 studies were reviewed in detail.

The studies by Hu et al. (2012), Ma et al. (2011), Luo et al. (2011), Hu et al. (2012a), Bye et al. (2012), Yuan et al. (2011), and Gu et al. (2012) were excluded because of insufficient clinical information on IHC. The studies of Wang et al. (2011) and focused on colorectal cancer. After the nine studies were excluded, seven studies met the criteria for inclusion (Figure 1). These studies were published between 2011 and 2014. All studies were from China and involved 761 esophageal and gastric cancer cases and 457 controls. The sample sizes ranged from 100 to 279 patients. PLCE1 expression was evaluated by IHC in all studies. Table 1 shows the detailed outline

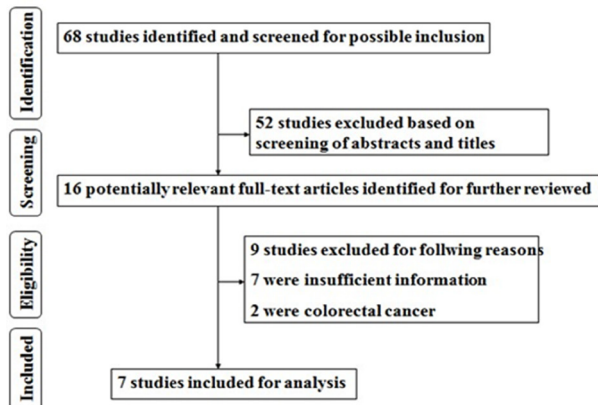


Figure 1. Flow Diagram of Identifying Potential Studies in Our Meta-analysis

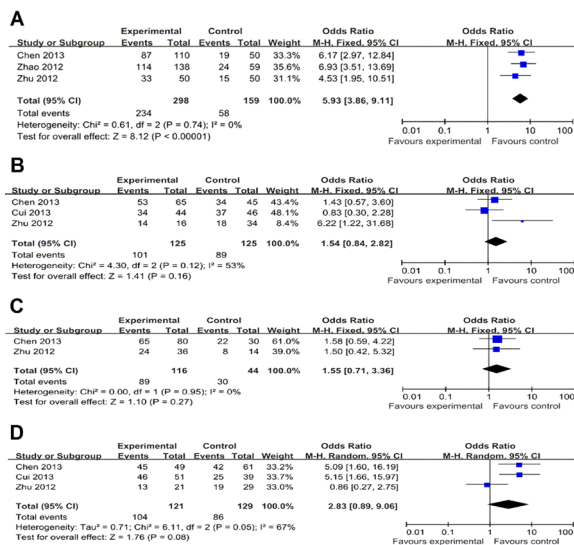


Figure 2. Forrest Plot of Odds Ratios (ORs) for the Association of PLCE1 Expression in Esophageal Cancer with Clinicopathological Features. A) tumor progression, B) invasion depth, C) histologic grade, D) lymph node metastasis

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

| First author | Year | Ethnicity(Nationality) | Cancer diagnosis | No. of Cases/Controls | Ages(mean) | Method |
|--------------|------|------------------------|--------------------------|-----------------------|--------------|--------|
| Wu | 2011 | Chinese(Han) | Histologically confirmed | 156/123 | 32~80(56) | IHC |
| Liang | 2012 | Chinese(Han) | Histologically confirmed | 97/97 | 31~78(56) | IHC |
| Zhang | 2012 | Chinese(Han) | Pathologically confirmed | 120/30 | Not shown | IHC |
| Chen | 2013 | Chinese(Kazakh) | Pathologically confirmed | 110/50 | Not shown | IHC |
| Zhu | 2012 | Chinese(Han) | Pathologically confirmed | 50/50 | 36~76(60.08) | IHC |
| Zhao | 2012 | Chinese(Han) | Pathologically confirmed | 138/59 | Not shown | IHC |
| Cui | 2014 | Chinese(Kazakh) | Pathologically confirmed | 90/48 | Not shown | IHC |

of the parameters of the included studies on esophageal and gastric cancers.

Pooled analyses

Esophageal cancer: Four studies examining esophageal cancer were included for the evaluation of association with PLCE1 expression. Figure 2A shows that PLCE1 expression was associated with tumor progression (pooled OR=5.93; 95%CI=3.86 to 9.11). The pooled OR indicated no significant association between PLCE1 expression and invasion depth (T3/4 versus T1/2) (pooled OR=1.54; 95%CI=0.84 to 2.82) (Figure 2B). Moreover, the current analysis failed to determine any significant association between PLCE1 expression and histologic grade (pooled OR=1.55; 95%CI=0.71 to 3.36) (Figure 2C) or lymph node metastasis (pooled OR=2.83; 95%CI=0.89 to 9.06) (Figure 2D).

Gastric cancer

Three gastric cancer studies were used to assess the relationship between PLCE1 and clinical characteristics of patients with gastric cancer. Figure 3A shows that a significant association between PLCE1 expression and tumor progression (pooled OR=9.73; 95%CI=6.46 to 14.66). A significant association between PLCE1 expression and histologic grade was determined, as shown in Figure 3B (pooled OR=3.85; 95%CI=2.46 to 6.04). Invasion depth (T3/4 versus T1/2) (pooled OR=3.62;

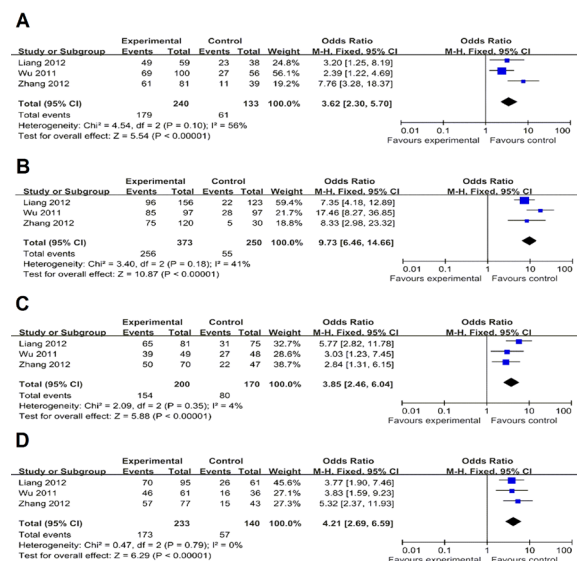


Figure 3. Forrest Plot from the Meta-analysis of PLCE1 Expression and the Risk of Gastric Cancer Stratified by Clinical Characteristic. A) tumor progression, B) histologic grade, C) invasion depth, D) lymph node metastasis

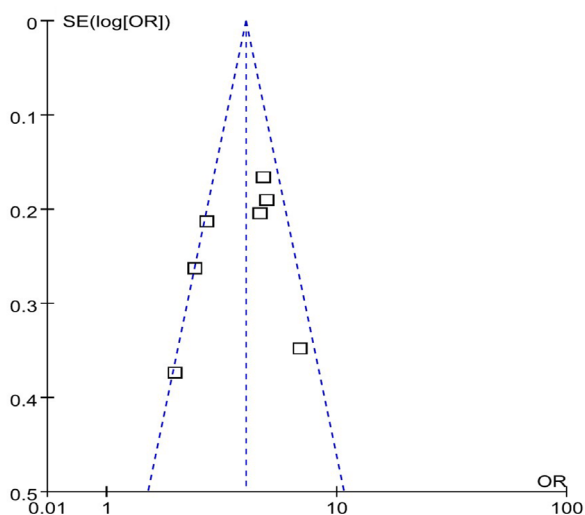


Figure 4. Begg's Funnel Plot Estimated the Publication Bias of the Included Literatures

95%CI=2.30 to 5.70) (Figure 3C) and lymph node metastasis (pooled OR=4.21; 95%CI=2.69 to 6.59) (Figure 3D) are also determined to be associated with PLCE1 expression. No obvious publication bias was observed (Figure 4) in both gastric and esophageal cancers.

Discussion

PLCE1 functions as an effector of guanosine triphosphatases (Ras, Rap1, and Rap2), which are involved in the regulation of cell growth, differentiation, apoptosis, and angiogenesis (Song et al., 2001). Recent studies have shown that PLCE1 may serve a critical function in the carcinogenesis process of esophageal and gastric cancers (Yu et al., 2014; Zhao et al., 2014) and have identified its involvement in various cancers, such as carcinoma of bladder (Ou et al., 2010), colorectal (Wang et al., 2012b), head and neck (Bourguignon et al., 2006), and skin (Bai et al., 2004) cancers. In previous studies of esophageal and gastric cancers, increased PLCE1 expression was significantly correlated with invasion depth, lymph node metastasis, and histologic grade. However, conflicting results have been reported from different laboratories. For example, Zhu et al. (2012) did not find a relationship between PLCE1 expression and lymph node metastasis, which is contrary to the result of Chen et al. (2013) and Hu et al. (2012b). Thus, we conducted the current meta-analysis to clarify such inconsistencies. To our knowledge, this meta-analysis is the first study to estimate PLCE1 expression systematically, as well as assess its relationship with the clinicopathological characteristics of patients. In the current study, we determined that PLCE1 expression was associated with tumor progression in both esophageal and gastric cancers. Moreover, the invasion depth and the lymph node metastasis were correlated with PLCE1 expression in gastric cancer.

Whether PLCE1 over-expression could be considered as a prognostic factor for esophageal cancer patients remains disputed. Several researchers reported that PLCE1 expression was reduced in ESCC tissues, suggesting that PLCE1-positive expression decreased progressively with the depth of tumor invasion and advancing stage of

esophageal cancer. However, our previous study indicated that the up-regulation of PLCE1 was involved in cancer metastasis and aggressiveness in Kazakh patients with ESCC. In the current meta-analysis, we determined the significant association of the *p*-TNM stage of tumor with PLCE1 overexpression is higher than that of the *p*-TNM stage of tumor without PLCE1 overexpression. These results indicated that PLCE1 may affect human esophageal cancer progression and that PLCE1 was an independent prognostic indicator for esophageal carcinoma. Our study also showed that no significant correlation between PLCE1 and clinicopathological parameters, such as invasion depth, histologic grade, and lymph node metastasis in esophageal cancer. However, PLCE1 expression was associated with tumor progression in two Kazakh groups in the study of Chen and Cui et al. (2013; 2014b), but not in another Kazakh group in the study of Zhu et al. (2012). This result suggests that ethnicity population heterogeneity may influence gene expression. The conflicting results may also be caused by the limited number of the two Kazakh populations, which had insufficient statistical power to detect a slight effect. Further well-designed extensive studies are needed to confirm the credibility of the result of the current meta-analysis.

In the study of Wang et al. (2012b), PLCE1 can function as a tumor-suppressor gene and PLCE1 overexpression significantly inhibited the proliferation of colon cancer cells and degraded its malignant degree. However, there previous results showed that PLCE1-positive expression had a significant correlation with clinical stage and lymph node metastasis of gastric cancer (Wu, 2011; Liang, 2012; Zhang et al., 2012), which was in accordant with the current meta-analysis that PLCE1 overexpression, as detected by IHC, was significantly associated with invasion depth, histologic grade, lymph node metastasis, and tumor progression in gastric cancer. The conclusion is that PLCE1 expression was a precursor of gastric carcinoma and served as a reliable tumor marker in gastric cancer. However, the precise mechanism of the increased PLCE1 expression in gastric cancer remains unclear. PLCE1 contains several Ras binding domains for small G-proteins of the Ras family and is downstream of the Ras superfamily GTPases (Ras, Rap1 and Rap2) involved in regulating cell growth, differentiation, apoptosis and angiogenesis (Bunney et al., 2009). Invasion of cancer cells in the blood and lymphatic vessels is a critical point for cancer metastasis. Indirect evidence for this condition is provided by a report indicating that PLCE1 serves an oncogenic function in intestinal carcinogenesis through the augmentation of inflammatory signaling pathways and angiogenesis (Li et al., 2009). One of the vital mechanisms of angiogenesis promoted by PLCE1 seems to be relevant to its function in the induction of VEGF expression, which is one of the important angiogenic factors and necessary constituents for tumorigenesis and metastasis (Carmeliet et al., 2000; Bergers et al., 2003). Based on these findings, PLCE1 expression may alter the motility of esophageal and gastric cancer cells through the same signaling pathway. This result appears to provide reasonable explanations for the results of the current study

that overexpressed PLCE1 may be involved in metastasis and aggressiveness of gastric cancer.

Several potential limitations of this meta-analysis should be considered. First, this study was restricted to papers published in English and Chinese, which could have introduced bias to our results. Second, the majority of the studies involved were from China, thus, the result is only a reflection of the situation in this country. Third, the judgment standards of PLCE1 expression are objective, although the results are still subjective because of the assessments of the examiners.

In summary, the findings of this meta-analysis indicate that PLCE1 overexpression is significantly associated with an increased risk of ESCC and GCA. Therefore, PLCE1 expression is appropriately regarded as a promising diagnosis biomarker for ESCC and GCA patients. However, the basis of our conclusion is only applicable to the Chinese Han and Kazakhs and not to other population groups. More studies are needed to investigate further the association of PLCE1 expression across different ethnic populations. Therefore, extensive and well-designed prospective studies are required to confirm our results further.

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