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
Xiao-Bin Cui et al (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 rs22744223 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 PLCE1mRNA 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). F statistic 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 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;
Bias of the Included Literatures

Figure 4.

with the depth of tumor invasion and advancing stage of 

expression was reduced in ESCC tissues, suggesting 

remains disputed. Several researchers reported that PLCE1 

as a prognostic factor for esophageal cancer patients 

expression systematically, as well as assess its relationship 

the current study, we determined that PLCE1 expression 

this meta-analysis is the first study to estimate PLCE1 

metastasis (pooled OR=4.21; 95%CI=2.69 to 6.59) (Figure 

expression. No obvious publication bias was observed 

Both gastric and esophageal cancers.

Discussion

PLCE1 functions as an effector of guanosine 

tri phosphatases (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 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 
ode 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 tumorgenesis and 
metastasis (Carmeliet et al., 2000; Berget 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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References

Abnet CC, Freedman ND, Hu N, et al (2010). A shared susceptibility locus in PLCE1 at 10q23 for gastric adenocarcinoma and esophageal squamous cell carcinoma. Nature genetics, 42, 764-7.

Baertschiger RM, Serre-Beinier V, Morel P, et al (2009). Fibrogenic potential of human multipotent mesenchymal stromal cells in injured liver. PloS one, 4, 6657.

Bai Y, Edamatsu H, Maeda S, et al (2004). Crucial role of phospholipase C epsilon in chemical carcinogen-induced skin tumor development. Cancer Res, 64, 8808-10.

Bergers G, Benjamin LE (2003). Tumorigenesis and the angiogenic switch. Nature Reviews Cancer, 3, 401-10.

Bourguignon LY, Gilad E, Brightman A, et al (2006). Hyaluronan-CD44 interaction with leukemia-associated RhoGEP and epidermal growth factor receptor promotes Rho/Ras co-activation, phospholipase C epsilon-Ca2+ signaling, and cytoksetol modulation in head and neck squamous cell carcinoma cells. J Biol Chem, 281, 14026-40.

Bunney TD, Baxendale RW, Katan M (2009). Regulatory links between PLC enzymes and Ras superfamily GTases: Signalling via PLCε. Adv Enzyme Regul, 49, 54-8.

Bye H, Prescott NJ, Lewis CM, et al (2012). Distinct genetic association at the PLCE1 locus with oesophageal squamous cell carcinoma in the South African population. Carcinogenesis, 33, 2155-61.

Cui XB, Chen YZ, Pang XL, et al (2013). Multiple polymorphisms within the PLCE1 are associated with esophageal cancer via promoting the gene expression in a Chinese Kazakh population. Gene, 530, 315-22.

Cui XB, Zhao ZM, Liu D, et al (2014a). Inactivation of miR-34a by aberrant CpG methylation in Kazakh patients with esophageal carcinoma. J Exp Clin Canc Res, 33, 20.

Cui XB, Pang XL, Li S, et al (2014b). Elevated expression patterns and tight correlation of the PLCE1 and NF-xb signaling in Kazakh patients with esophageal carcinoma. Medical Oncol, 31, 791.

Danielsen SA, Cekaite L, Agenes TH, et al (2011). Phospholipase C isozymes are deregulated in colorectal cancer-insights gained from gene set enrichment analysis of the transcriptome. PloS one, 6, 24419.

Gonzalez-Garcia A, Pritchard CA, Paterson HF, et al (2005). RaLGD5 is required for tumor formation in a model of skin angiogenesis. Cancer cell, 7, 219-26.

Gu H, Ding G, Zhang W, et al (2012). Replication study of PLCE1 and C20orf54 polymorphism and risk of esophageal cancer in a Chinese population. Mol Biol Rep, 39, 9105-11.

Hu H (2012). Roles of genetic polymorphism and mutation in esophageal squamous cell carcinoma (ESCC) and non-small cell lung cancer (NSCLC)[D]. CHINA: Fudan University, 28-41.

Hu H, Yang J, Sun Y, et al (2012). Putatively functional PLCE1 variants and susceptibility to esophageal squamous cell carcinoma (ESCC): a case-control study in eastern Chinese populations. Ann Surg Oncol, 19, 2403-10.

Islami F, Boffetta P, Ren J-S, et al (2009). High-temperature beverages and foods and esophageal cancer risk-A systematic review. Int J Cancer, 125, 491-524.

Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. CA Cancer J Clin, 61, 69-90.

Li M, Edamatsu H, Kitazawa R, et al (2009). Phospholipase C epsilon promotes intestinal tumorigenesis of Apc (Min/+) mice through augmentation of inflammation and angiogenesis. Carcinogenesis, 30, 1424-32.

Liang Q (2012). Expression of PLCE1 in gastric cancer and its effect on cell cycle and apoptosis of gastric cancer cells. CHINA:HuaZHong University of Science & Technology, 14-22.

Luo D, Gao Y, Wang S, et al (2011). Genetic variation in PLCE1 is associated with gastric cancer survival in a Chinese population. J Gastroenterol, 46, 1260-6.

Luo XP (2014). Phospholipase C epsilon-1 inhibits p53 expression in lung cancer. Cell Biochem Funct, 32, 294-8.

Ma H, Wang LE, Liu Z, et al (2011). Association between novel PLCE1 variants identified in published esophageal cancer genome-wide association studies and risk of squamous cell carcinoma of the head and neck. BMC Cancer, 11, 258.

Malik MA, Umar M, Gupta U, et al (2014). Phospholipase C epsilon 1 (PLCE1 rs2274223A>G, rs765524C>T and rs7922612C>T) polymorphisms and esophageal cancer risk in the Kashmir valley. Asian Pac J Cancer Prev, 15, 4319-23.

Mbuliaye SM, Hisada M, El-Omar EM (2009). Helicobacter pylori associated global gastric cancer burden. Frontiers in
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Bioscience: a J Virtual Library, 14, 1490.

Ou L, Guo Y, Luo C, et al (2010). RNA interference suppressing PLCE1 gene expression decreases invasive power of human bladder cancer T24 cell line. Cancer genetics and cytogenticics, 200, 110-9.

Ren J (2011). Family history and genetic susceptibility to gastric cardia adenocarcinoma of Chinese Han population. CHINA:Zhengzhou University, 43-7.

Rhee SG (2001). Regulation of phosphoinositide-specific phospholipase C*. Ann Review Biochemistry, 70, 281-312.

Song C, Hu CD, Masago M, et al (2001). Regulation of a novel human phospholipase C, PLCepsilon, through membrane targeting by Ras. J Biol Chem, 276, 2752-7.

Tran GD, Sun XD, Abnet CC, et al (2005). Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. Int J Cancer, 113, 456-63.

Wang L-D, Zhou F-Y, Li X-M, et al (2010). Genome-wide association study of esophageal squamous cell carcinoma in Chinese subjects identifies susceptibility loci at PLCE1 and C20orf54. Nature Genetics, 42, 759-63.

Wang M, Zhang R, He J, et al (2012). Potentially functional variants of PLCE1 identified by GWASs contribute to gastric adenocarcinoma susceptibility in an eastern Chinese population. PLoS One, 7, 31932.

Wang X, Zhou C, Qiu G, et al (2007). Screening of new tumor suppressor genes in sporadic colorectal cancer patients. Hepato-gastroenterol, 55, 2039-44.

Wang X, Zhou C, Qu G, et al (2011). Phospholipase C epsilon plays a suppressive role in incidence of colorectal cancer. Medical Oncology, 29, 1051-8.

Wing MR, Bourdon DM, Harden TK (2003). PLC-epsilon: a shared effector protein in Ras-, Rho-, and G alpha beta gamma-mediated signaling. Molecular Interventions, 3, 273-80.

Wu L (2011). The expression and significance of PLCE1 in gastric cancer.[D]. CHINA:Huaqiong University of Science and Technology, 11-23.

Wu M, Liu AM, Kampman E, et al (2009). Green tea drinking, high tea temperature and esophageal cancer in high- and low-risk areas of Jiangsu Province, China: A population-based case-control study. Int J Cancer, 124, 1907-13.

Yu S, Wu F, Guo K, et al (2014). Expression of phospholipase C epsilon-1 in gastric cancer and its association with prognosis. Zhonghua Wei Chang Wai Ke Za Zhi, 17, 378-82.

Zhang W, Su L, Jun-hui C, et al (2012). Expression of phospholipase C epsilon-1 in locations of different parts gastric cancers. henan medical research, 21, 399-402.

Zhao L, Wei Z-B, Yang C-Q, et al (2014). Effects of PLCE1 gene silencing by RNA interference on cell cycling and apoptosis in esophageal carcinoma cells. Asian Pac J Cancer Prev, 15, 5437-42.

Zhao X, Zhou F, Zhang L, et al (2012). Expression of PLCE1 protein in esophageal multistage carcinogenesis. J Henan University:Med Sci, 31, 203-5.

Zhu J, Yin L, Hou L, et al (2012). Expression characteristics and significance of PLCE1 in esophageal squamous cell carcinoma of xinjiang kazakh. J Nongken Med, 5-8.