RESEARCH ARTICLE

Loss of Expression of PTEN is Associated with Worse Prognosis in Patients with Cancer

Zhi-Xin Qiu[1&], Shuang Zhao[1&], Lei Li[1], Wei-Min Li[1*]

Abstract

Background: The tumor suppressor phosphatase and tensin homolog (PTEN) is an important negative regulator of cell-survival signaling. However, available results for the prognostic value of PTEN expression in patients with cancer remain controversial. Therefore, a meta-analysis of published studies investigating this issue was performed. Materials and Methods: A literature search via PubMed and EMBASE databases was conducted. Statistical analysis was performed by using the STATA 12.0 (STATA Corp., College, TX). Data from eligible studies were extracted and included into the meta-analysis using a random effects model. Results: A total of 3,810 patients from 27 studies were included in the meta-analysis, 22 investigating the relationship between PTEN expression and overall survival (OS) using univariate analysis, and nine with multivariate analysis. The pooled hazard ratio (HR) for OS was 1.64 (95% confidence interval (CI): 1.32-2.05) by univariate analysis and 1.56 (95% CI: 1.20-2.03) by multivariate analysis. In addition, eight papers including two disease-free-survival analyses (DFSs), four relapse-free-survival analyses (RFSs), three progression-free-survival analyses (PFSs) and one metastasis-free-survival analysis (MFS) reported the effect of PTEN on survival. The results showed that loss of PTEN expression was significant correlated with poor prognosis, with a combined HR of 1.74 (95% CI: 1.24-2.44). Furthermore, in the stratified analysis by the year of publication, ethnicity, cancer type, method, cut-off value, median follow-up time and neoadjuvant therapy in which the study was conducted, we found that the ethnicity, cancer type, method, median follow-up time and neoadjuvant therapy are associated with prognosis. Conclusions: Our study shows that negative or loss of expression of PTEN is associated with worse prognosis in patients with cancer. However, adequately designed prospective studies need to be performed for confirmation.

Keywords: Cancer - PTEN - overall survival - meta-analysis

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Introduction

The global burden of cancer continues to increase dramatically with approximately 12.7 million new cancer cases and 7.6 million cancer-related deaths every year worldwide (Jemal et al., 2011). Due to a major part of patients diagnosed with advanced stage and die as a result of cancer metastases resistant to conventional therapy, the overall survival for patients with cancers is still with a very low proportion.

Tumor occurrence and development is a multi-step and complex process that influenced by various environment and genetic factors. Nowadays, several biological markers have been recognized as prognosticators, as well as indicator of potential therapeutic targets for different types of human cancers. Owing to the complicated molecular biology, multiple factors including the cell growth, cell cycle control, angiogenesis, morphogenesis, apoptosis, and metastatic adhesion have been researched with the aim of creating biological risk assessment and biological staging models for cancers (Al-Saad et al., 2008). The tumor suppressor phosphatase and tensin homolog (PTEN) is an important negative regulator of cell-survival signaling (Sawai et al., 2008), it's involved in the regulation of cell growth, proliferation, and apoptosis in signal transduction pathways and participates in the control of cell cycle (Yin et al., 2008; Ortega-Molina et al., 2013). Recently, some evidences to suggest that loss of expression of PTEN have adverse association with prognostic value, but some other researches showed no correlation. Additionally, underexpression of PTEN confers resistance to cetuximab-induced apoptosis (Loupakis et al., 2009). Therefore, investigate the relationship between the expression of PTEN and the prognosis of patients with cancers is important, as this will be helpful for adopting appropriate targeted therapy.

However, the relationship of PTEN expression levels to cancer patients' survival remains to be controversial. Therefore, based on the discordant results obtained by numbers of studies, we conducted this meta-analysis to quantify the role of PTEN as prognostic marker among patients with cancer.

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Materials and Methods

Literature search

A literature search via PubMed and EMBase databases was conducted to find articles that evaluated the role of PTEN in cancer (Last search was updated on Jan 13, 2015) using the following keywords and text words: *i)* Phosphatase and tensin homolog or PTEN, and *ii)* cancer, and *iii)* survival analysis or prognostic, and *iv)* expression, and *v)* tissue.

Selection criteria

The language in which the articles were written was not restricted, and all eligible studies that examined the association between the expression of PTEN and overall survival (OS) or any other survival analysis were gathered. However, the papers which only have abstracts were excluded because of insufficient data for meta-analysis. Therefore, we first carefully read the titles and abstracts of the publications to find exactly those studies that indeed examined the relationship between the expression of PTEN and OS or other survival analysis in patients with cancer. After the abstracts met these conditions, the full texts were analyzed and included into our meta-analysis according to the following criteria: *i)* articles were written as full paper; *ii)* expression levels of PTEN were compared to patient's OS or other survival analysis; *iii)* expression of the proteins were evaluated in tumor tissues by immunohistochemistry (IHC) or reverse transcription and polymerase chain reaction (RT-PCR) analysis; *iv)* Hazard ratios (HR) and 95%CI for survival were provided or could be calculated from the sufficient data; *v)* if the same group of patients were used to analyze more than once, the most complete research was selected for our study.

Data extraction

Two investigators (Zhi-Xin Qiu and Shuang Zhao) checked all potentially relevant articles and extracted data in separate databases. In case of disagreement, a third author (Lei Li) would assess these articles. The following information were collected from each study: first author's name, year of publication, ethnicity, number of patients, laboratory methodology, median follow-up time, cut-off value, information about neoadjuvant therapy, histological type, lymph node metastasis, clinical stage and HR with 95%CI.

Statistical analysis

The intensity of relationship between the expression levels of PTEN and survival were described as HRs. Negative expression of PTEN indicated poor prognosis in patients with cancer if HR>1 with the 95%CI did not overlap 1. From some published researches, HR and 95%CI could be directly obtained by using univariate or multivariate survival analysis. Otherwise, HR and 95%CI were calculated by Kaplan-Meier survival curves using the software Engauge Digitizer Version 4.1 (http://digitizer.sourceforge.net/) and the method presented by Parmar et al. before (Parmar et al., 1998). Then, extracted data were utilized to reconstruct the HR and its variance (GraphPad Software, Inc, La Jolla, CA, USA).

The pooled HR corresponding to the 95%CI was used to assess the prognostic value of PTEN in patients. Statistical heterogeneity was tested by Cochrane's Q test (Chi-squared test; Chi2) and inconsistency (I2) (Lau et al., 1997; Higgins et al., 2002). If there was no obvious heterogeneity, the fixed-effects model (Mantel-Haenszel method) was used to estimate the pooled HR; otherwise, the random-effects model (DerSimonian and Laid method) was used. Funnel plot and Begg's rank correlation method were designed for assessing risk of publication bias. STATA 12.0 (STATA Corp., College, TX) was used to perform statistical analysis. A P-value less than 0.05 was consider to be statistically significant.

Results

Study Selection and Characteristics

164 and 78 articles were retrieved from PubMed and EMBase electronic database according to our defined keywords and text words, respectively (Figure 1). Then, via careful reading the abstracts, 51 researches that focused on the association between the expression of PTEN and survival were included in our full-text review process. After reading the full-text researches, 24 papers had to be excluded because data were not extractable or could not provide enough information about survival. Finally 27 studies including 3810 cases were available for our meta-analysis. All the included studies were in English.

The individual characteristic of the eligible researches are summarized in Table 1, 11 studies included patients from Asia, nine from America, two form United Kingdom, two from Germany, one from Portland, one from Australia and one from Australia respectively. Among all the included studies, three papers about breast cancer, six papers about colorectal cancer, three papers about gastric carcinoma, four papers about prostate cancer, two papers about lung cancer and nine papers about other cancer types. Expressions of PTEN were detected via IHC, Taqman, TMA or RT-PCR. 23 articles evaluated the relationship between PTEN expression and OS, 10 articles evaluated the relationship between PTEN expression and other survival analysis that including DFS, PFS, MFS

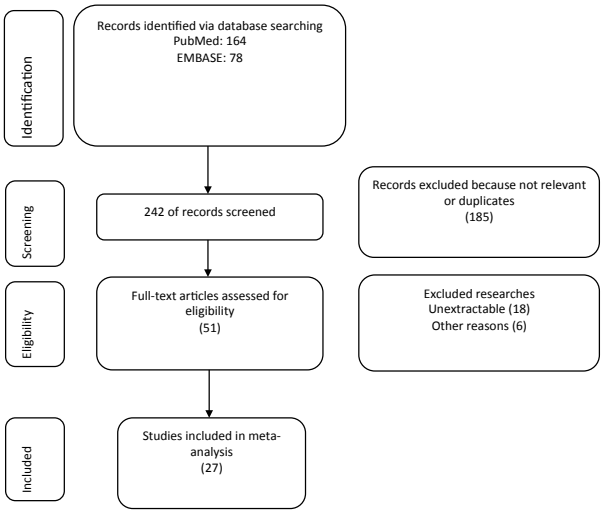

Figure 1. Flow Chart Summarizing the Literature Search and Study Selection

Table 1. Main Characteristics and Results of Eligible Studies

First Author	Year	Ethnicity	Cancer type	Cases	P/N	Method	Cutoff-value	Median Follow-up Time	Neoadjuv-ant Therapy	Histological Type	Lymph Node Metastasis (Yes/No)	Diff (Well and moderate/ poor)	
Ferraldeschi	2015	British	Prostate Cancer	144	87/57	IHC	scores>0	55M	Yes	NA	NA	NA	NA
Kessler	2015	German	Glioblas-toma	79	37/42	IHC	>1% cell	15M	Yes	NA	NA	NA	NA
Martins	2014	British	Ovarian cancer	228	117/111	IHC	NA	200M	NA	High-grade serous	NA	NA	NA
Barnett	2014	Portland	Prostate Cancer	48	31/17	IHC	NA	109M	NA	NA	9/39	NA	
Wu	2013	American	Breast cancer	65	35/30	IHC,	>5% cell	60M	NA	IDC/ILC /DCIS	NA	NA	NA
Atreya	2013	American	Colorectal cancer	50	43/7	IHC	>90% cell	28M	Yes	NA	NA	NA	NA
Yin Li	2013	Chinese	Gastric carcinoma	114	47/67	IHC	scores>4	60M	Yes	NA	74/40	67/47	
Hong Yan Zhang	2013	Chinese	Breast cancer	146	84/62	IHC	>0%cell	103M	NA	NA	99/47	NA	
Timothy J. Price	2013	Australia	Colorectal cancer	302	185/117	Taqman	NA	30.6M	Yes	NA	NA	NA	NA
Minmin Song	2013	Chinese	Colorectal cancer	404	365/39	IHC, qRT-PCR	NA	60M	NA	NA	NA	NA	NA
Fu-neng Jiang	2013	Chinese	Prostate cancer	112	36/66	IHC	NA	100M	NO	NA	28/84	NA	
Xuehua Zhu	2013	Chinese	Gastric carcinoma	159	61/98	TMA	IRS>0	36M	NO	NA	123/36	NA	
S Boeck	2013	German	Pancreatic cancer	171	141/30	IHC	scores>4	30M	NA	NA	NA	NA	NA
Nilda D. Gonzalez-Roibon	2013	American	Urothelial carcinoma	19	14/5	IHC	H scores	242D	NA	NA	2/4	NA	
Yu-Mei Liang	2012	Chinese		104	61/43	TMA	>10%cell	33M	NA	NA	15/89	NA	NA
Arjun Sood	2012	American	Colorectal cancer	76	32/44	IHC	>50% cell	62.5M	Yes	NA	NA	NA	NA
Nokitaka Setsu	2012	Japanese	Soft tissue	111	89/22	IHC	scores>1	150M	Yes	NA	NA	NA	NA
Akihiko Yoshizawa	2010	American	Non-small cell lung cancer	267	250/17	IHC	>TS2	60M	NO	137/128 (ADC/SCC)	NA	NA	NA
Joon-Yong Chung	2009	Korean	Extrahepatic	134	117/17	TMA	NA	60M	NA	NA	74/147	NA	
Hirozumi Sawai	2008	Japanese	Colorectal cancer	69	52/17	IHC	Group W	60M	Yes	NA	NA	67/2	
Evangelia Razis	2008	Greek	Colorectal cancer	72	62/10	IHC	>10%cell	53M	Yes	NA	NA	NA	
Halldora K.	2008	American	Gliomas	85	56/29	IHC	scores>2	48M	NO	63/22 (LGG/HGG)	NA	NA	NA
Roble Bedolla	2007	American	Prostate cancer	65	51/14	IHC	scores>0	NA	Yes	NA	NA	NA	
Allan J. Pantuck	2007	American	Renal cell carcinoma	375	360/15	IHC	scores>3	56.9M	NA	323/40/12 (clear cell /papillary /others)	52/323	NA	v
Huachuan Zheng	2007	Japanese	Lung carci-noma	155	82/73	IHC		20.6M	NA	37/86/14/18 (SCC/ADC/ LCC/SQ)	53/102	NA	
Tsung-Hui Hu	2002	Chinese		105	43/62	IHC	scores>0	147M	NA	NA	NA	78/27	
Peter L. Depowski	2001	American	Breast cancer	151	93/58	IHC	NA	59M	NA	104/47(ductal/ lobular)	74/63	25/75	

*P/N, positive expression/negative expression; IHC, immunohistochemistry; TMA, tissue microassay; qRT-PCR, quantitative reverse transcription; IDC, Infiltrating ductal; ILC, Lobular carcinoma; DCIS, Ductal lobular carcinoma situ; LGG, Low-grade gliomas; HGG, High-grade gliomas; SCC, Small cell carcinoma; ADC, Adenocarcinoma; LCC, Large cell carcinoma; SQ, Squamous cell carcinoma; M, month; NA, no available or no applicable.

and RFS. According to univariate analysis in OS, 10 studies provided the HR with 95%CI directly, 12 studies showed survival curves that available to calculate the HR. Additionally, nine studies provided the HR with 95%CI directly, the other 14 papers had no data available by multivariate analysis (Table 2).

Meta-analysis

First of all, we evaluated whether PTEN expression levels were associated with the OS in patients with cancer.

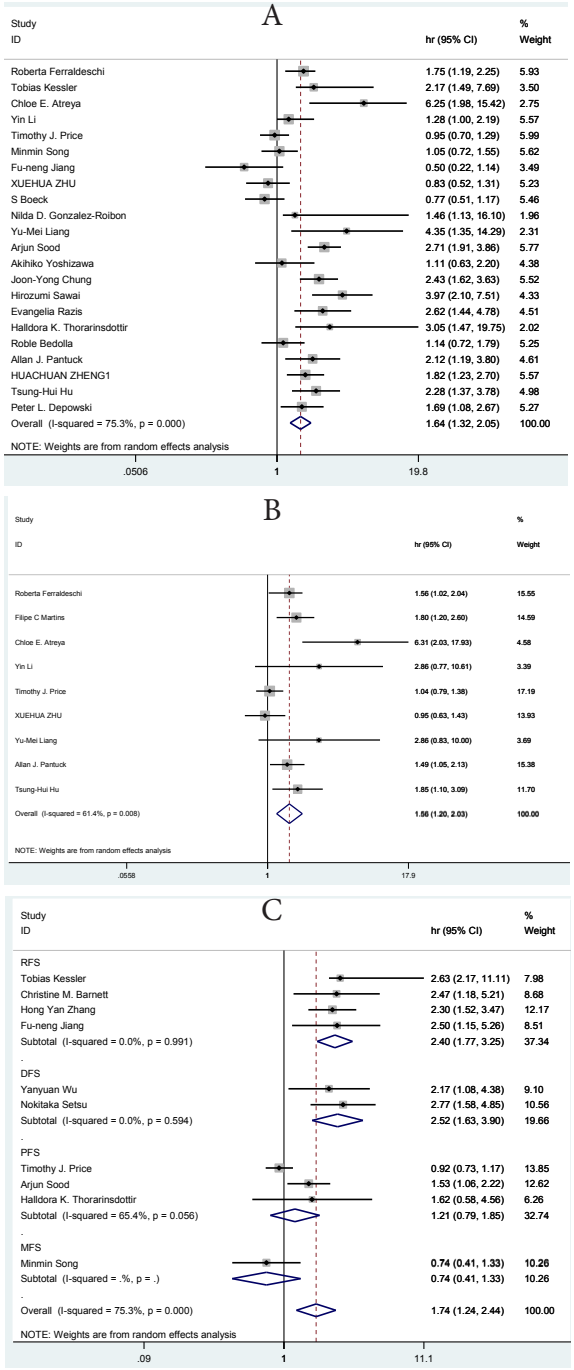

Figure 2. A) Forest Plot Showing the Combined relative HR from the Random-Effects Model for Overall Survival By Univariate Analysis. (B) Forest plot showing the combined relative HR from therandom-effects model for overall survival by multivariate analysis. **(C).** Forest plot showing the combined relative HR from the random-effects model for overall survival by other survival analysis

Of the 23 trials evaluable for systematic review, 14 articles could not be included in meta-analysis by multivariate analysis due to insufficient data to estimate the HR and 95%CI.

A total of 22 studies, including 3212 patients, reported the effect of PTEN on OS using analyses unadjusted for other factors (Depowski et al., 2001; Hu et al., 2003; Zheng et al., 2007; Pantuck et al., 2007; Bedolla et al., 2007; Sawai et al., 2008; Thorarinsdottir et al., 2008; Razis et al., 2008; Sawai et al., 2008; Chung et al., 2009; Yoshizawa et al., 2010; Sood et al., 2012; Liang et al., 2012; Gonzalez-Roibon et al., 2013; Boeck et al., 2013; Zhu et al., 2013; Jiang et al., 2013; Song et al., 2013; Price et al., 2013; Li et al., 2013; Atreya et al., 2013; Ferraldeschi et al., 2015; Kessler et al., 2015). As shown in Figure 2A, negative expression of PTEN was significantly correlated with worse OS according to univariate analysis, with a combined HR of 1.64 (95%CI: 1.32-2.05). The random-effects model (the DerSimonian and Laird method) was used because of significant heterogeneity was observed among these researches (p=0.000, I^2=75.3%). Nine studies, demonstrated the effect of PTEN on OS using analyses adjusted for other factors, including 1581 patients (Hu et al., 2003; Pantuck et al., 2007; Liang et al., 2012; Zhu et al., 2013; Price et al., 2013; Li et al., 2013; Atreya et al., 2013; Ferraldeschi et al., 2015; Martins et al., 2014). As shown in Figure 2B, statistically significant was observed between the expression of PTEN levels and OS, with a combined HR of 1.56 (95%CI: 1.20-2.03). The random-effects model (the DerSimonian and Laird method) was used because of significant heterogeneity was observed among these researches (p=0.008, I^2=61.4%). Furthermore, eight papers reported the effect of PTEN

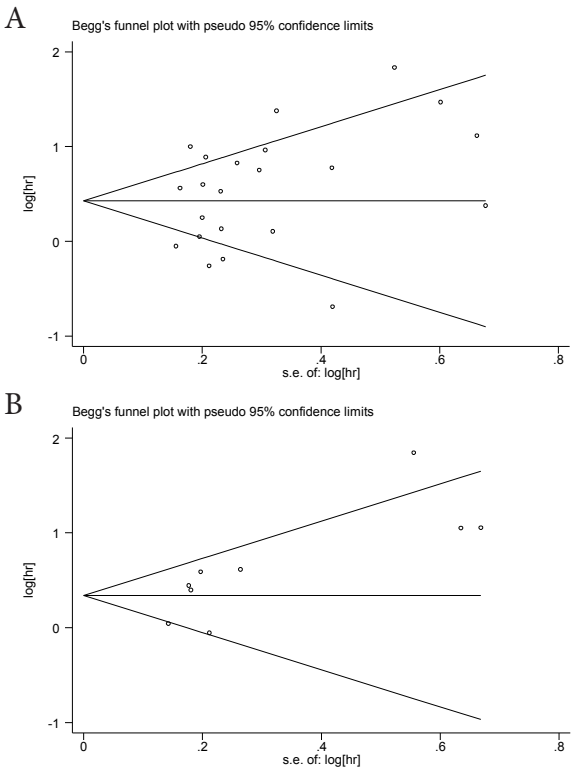

Figure 3. Funnel Blot was Designed to Visualize a Potential Publication Bias. A, univariate analysis; **B,** multivariate analysis

Table 2. Relationship between PTEN Expression and Survival

First Author	Ethnicity	Overall Survival						Other Survival Analysis					
		Univariate			Multivariate			Univariate			Multivariate		
		HR Estimate	HR	95% CI	HR	HR	95% CI	HR Estimate	HR	95% CI	HR	HR	95% CI
Ferraldeschi	British	HR 95%CI	1.75	1.19-2.25	HR 95%CI	1.6	1.02-2.04	NA	NA	NA	NA	NA	NA
Kessler	German	HR 95%CI	2.17	1.49-7.69	NA	NA	NA	(RFS)HR 95%CI	2.63	2.17-11.11	NA	NA	NA
Martins	British	NA	NA	NA	HR 95%CI	1.8	1.2-2.6	NA	NA	NA	NA	NA	NA
Barnett	Portland	NA	NA	NA	NA	NA	NA	HR 95%CI	2.47	1.18-5.21	NA	NA	NA
Wu	African American	NA	NA	NA	NA	NA	NA	(DFS)Sur. Curve	2.17	1.08-4.38	NA	NA	NA
	Hispanic/Latin	NA	NA	NA	NA	NA	NA	Sur. Curve	0.91	0.40-2.07	NA	NA	NA
Atreya	American	HR 95%CI	6.25	1.98-15.42	HR 95%CI	6.3	2.03-17.93	NA	NA	NA	NA	NA	NA
Li	Chinese	Sur. Curve	1.28	1.00-2.19	HR 95%CI		0.773-10.610	NA	NA	NA	NA	NA	NA
Zhang	Chinese	NA	NA	NA	NA	NA	NA	(RFS)Sur. Curve	2.3	1.52-3.47		0.786	0.595 1.037
Price	Australia	Sur. Curve	0.95	0.70-1.29	HR 95%CI	1.04	0.79-1.38	(PFS) Sur. Curve	0.92	0.73-1.17		0.9	0.7-1.16
Song	Chinese	Sur. Curve	1.05	0.72-1.55	NA	NA	NA	(MFS) Sur. Curve	0.74	0.41-1.33	NA	NA	NA
Jiang	Chinese	Sur. Curve	0.5	0.22-1.14	NA	NA	NA	(RFS) HR 95%CI	2.5	1.15-5.26		1.32	0.40-4.29
Zhu	Chinese	HR 95%CI		0.522-1.310	HR 95%CI		0.626-1.435	NA	NA	NA	NA	NA	NA
Boeck	German	HR 95%CI	0.77	0.51-1.17	NA	NA	NA	NA	NA	NA	NA	NA	NA
Gonzalez-Roibon	American	Sur. Curve	1.46	1.13-16.10	NA	NA	NA	NA	NA	NA	NA	NA	NA
Liang	Chinese	HR 95%CI	4.35	1.35-14.29	HR 95%CI	2.86	0.83-10	NA	NA	NA	NA	NA	NA
Sood	USA	Sur. Curve	2.71	1.91-3.86	NA	NA	NA	(PFS) HR 95%CI	1.53	1.06-2.22	NA	NA	NA
Setsu	Japanese	NA	NA	NA	NA	NA	NA	(DFS)Sur. Curve	2.77	1.58-4.85	NA	NA	NA
Yoshizawa	USA	HR 95%CI	1.11	0.63-2.20	NA	NA	NA	NA	NA	NA	NA	NA	NA
Chung	Korean	Sur. Curve	2.43	1.62-3.63	NA	NA	NA	NA	NA	NA	NA	NA	NA
Sawai	Japanese	Sur. Curve		2.10-7.51	NA	NA	NA	NA	NA	NA	NA	NA	NA
Razis	Greek	Sur. Curve		1.44-4.78	NA	NA	NA	NA	NA	NA	NA	NA	NA
Thorarinsdottir	USA	Sur. Curve		1.47-19.75	NA	NA	NA	(PFS) Sur. Curve	1.62	0.58-4.56	NA	NA	NA
Bedolla	USA	HR 95%CI		0.72-1.79	NA	NA	NA	NA	NA	NA	NA	NA	NA
Pantuck	American	Sur. Curve		1.19-3.80	HR	1.49	1.05-2.13	NA	NA	NA	NA	NA	NA
Zheng	Japanese	Sur. Curve		1.23-2.70	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hu	Chinese	HR 95%CI		1.37-3.78	HR	1.85	1.10-3.09	NA	NA	NA	NA	NA	NA
Depowski	American	HR 95%CI		1.08-2.67	NA	NA	NA	NA	NA	NA	NA	NA	NA

*HR, hazard ratio; CI, confidence interval; sur., survival; DFS, disease-free-survival; PFS, progression-free-survival; MFS, metastasis-free-survival; RFS, relapse-free-survival; NA, no available or no applicable

on other survival analysis using analyses unadjusted for other factors including four RFSs, three PFSs, two DFSs and one MFS (Barnett et al., 2014). As shown in Figure 2C, the results showed that loss of PTEN expression was significant correlated with poor prognostic, with a combined HR of 1.74 (95%CI: 1.24-2.44). The random-effects model (the DerSimonian and Laird method) was used because of significant heterogeneity was observed among these researches (p=0.000, I^2=75.3%).

Next, we performed subgroup analyses to investigate if there were differences in results with respect to the year of publication, ethnicity, cancer type, method, cut-off value, median follow-up time and neoadjuvant therapy in which the study was conducted. Despite the limited number of studies that were eligible for this meta-analysis, in the stratified analysis by ethnicity, increased risks were found for American (HR: 1.92, 95%CI: 1.35-2.74, p=0.0013) and Japanese (HR: 2.58, 95%CI: 1.21-5.51, p=0.041). Moreover, subgroup analyses regarding the cancer type and method of the study revealed that articles about colorectal cancer and IHC method showed a worse prognostic value for survival in patients with cancer (HR: 2.18, 95%CI: 1.25-3.78, p=0.000; HR: 1.75, 95%CI: 1.38-2.23, p=0.000 respectively). Additionally, subgroup analysis by median follow-up time of 60 months and neoadjuvant therapy with yes also showed loss of PTEN expression with poor prognostic (HR: 1.67, 95%CI: 1.06-2.63, p=0.001; HR: 1.95, 95%CI: 1.37-2.78, p=0.000). However, we couldn't get the statistically significant results from the other factors (Supporting Information Figure1-5). Because inadequate of researches, the stratified analysis on other survival analysis showed a trend that negative expression of PTEN with worse prognostic by DFS (HR: 2.52, 95%CI: 1.63-3.90, p=0.594) and RFS (HR: 2.40, 95%CI: 1.77-3.90, p=0.991). Thus, more studies should be conducted in the future.

Publication bias statistics were determined using the method of Begg's test. No publication biases were found in the 22 OS studies used for univariate analysis and nine OS studies used for multivariate analysis (p>0.05) (Figure 3). Sensitively analysis was performed to investigate the effect of every study on the overall meta-analysis by omitting one study each time, and the omission of any study made no significant difference, demonstrating that our results were statistically reliable.

However, we didn't investigated the relation of PTEN expression with clinicopathological variables because of insufficient clinicopathological information.

Discussion

There is a trend towards individualized treatment in tumor therapy. As we all known, immortalization and invasiveness are important characteristics for cancer tissues, and postoperative recurrence and metastasis are the principal causes for treatment failure and death in patients with cancers. Therefore, identifying the specific molecular markers to distinguish the high risk of disease recurrence and mortality in cancer patients is critical to monitor patients and select appropriate adjunctive therapies in clinical practice. However, several biological effectors related to cell growth, differentiation and adhesions have been studied in individuals who develop cancers. In previous studies, various kinds of genetic alterations have been identified as prognostic factors such as EGFR gene in NSCLC and HER-2 in breast carcinoma (Qiu et al., 2013). But, most other clinically useful molecular markers which have predictive value of the therapeutic response and prognostic value failed to demonstrate usefulness in subsequent investigations.

PTEN, a tumor suppressor has been firmly established. It is mapped to chromosome 10q23.3 (Song et al., 2012). The role of PTEN is to antagonizes the phosphoinositol-3-kinase (PI3K)/PTEN/AKT signaling pathway and suppresses cell survival and proliferation, thereby safeguard important cellular machineries against carcinogenesis (Wang et al., 2008; Sun et al., 2014). In addition, PTEN regulates a variety of biological processes including cell proliferation, growth, migration and death (Wang et al., 2008). Based on these reasons, we undertook a meta-analysis to determine whether PTEN can serve as a prognostic marker for patients with cancers.

Our meta-analysis focuses on the relationship between PTEN expression and survival of patients with cancer. This meta-analysis with accumulated data suggested that negative or loss of E-cadherin expression was associated with shorter survival time and predicted worse prognosis in patients with cancer. The pooled HR for OS was 1.64 (95%CI: 1.32-2.05) by univariate analysis and 1.56 (95%CI: 1.20-2.03) by multivariate analysis. Furthermore, small number of studies investigated the association between PTEN expression and other survival analyses including DFS, PFS, MFS and RFS, and also found that loss of PTEN expression was significant correlated with poor prognostic, with a combined HR of 1.74 (95%CI: 1.24-2.44). Interesting, after we did the stratified analysis, we found that increased risks were found for American (HR: 1.92, 95%CI: 1.35-2.74, p=0.0013) and Japanese (HR: 2.58, 95%CI: 1.21-5.51, p=0.041). Moreover, subgroup analyses regarding the colorectal cancer showed a worse prognostic value for survival in patients with cancer (HR: 2.18, 95%CI: 1.25-3.78, p=0.000).

Our meta-analysis is based on published data and was performed using univariate analysis followed by further multivariate analysis, which is the first time to evaluate the effect of PTEN on survival in different kinds of cancers. However, some limitations exist in our study. We did not include unpublished papers and abstracts into meta-analysis because the required data was available only in full publications. Additionally, the risks calculated in our meta-analysis may be an overestimate due to publication and reporting bias. Positive results tend to be accepted by journals, whereas negative results often are rejected or even not be submitted. Another potential source of bias is related to the method used to extrapolate the HR. HR was extracted from the data included in the article directly or calculated from the survival curves. Actually, the method of extrapolating HR from survival curves seems to be less reliable because this strategy did not completely eliminate inaccuracy in the extracted survival rates. Furthermore, we included studies with detection method by using IHC. As we known, prognostic markers based

on IHC can provide inconsistent or contradictory results, owing to the use of different antibodies and processing methods, as well as different scoring and categorization systems (Kase et al., 2000). It would be desirable to have IHC findings reported carefully and in detail. Moreover, we also think that different therapy strategies on patients after surgery in these studies have different impact on OS, thus this factor should be taken into consideration. Unfortunately, none of these studies has described the details of therapy strategy after the patients have diagnosed the cancer. Therefore, more meticulous research should be conducted. Nevertheless, no publication bias was detected using Begg's test (p>0.05), indicating that the statistics obtained approximate the actual results. Sensitivity analysis was also conducted to investigate the influence of a single study on the overall meta-analysis by omitting one study at a time, and the omission of any study made no significant difference, suggesting that our results were statistically reliable.

In summary, loss of E-cadherin expression was associated with worse OS in patients with cancers. Undoubtedly, these results should be confirmed by more prospective and randomized clinical studies, however, we provide new insights that support PTEN as a potential prognostic biomarker and biological target for anticancer therapies.

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