Loss of phosphatase and tensin homolog expression correlates with clinicopathological features of non-small cell lung cancer patients and its impact on survival: A systematic review and meta-analysis

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Abstract

Background: Phosphatase and tensin homolog (PTEN), regarded as a tumor suppressor gene, may act as a prognostic biomarker in human cancers.

Methods: All eligible studies from MEDLINE, Embase, CENTRAL, and the Chinese BioMedical Literature Database to October 2016 were incorporated. Two reviewers independently screened the literature according to inclusion and exclusion criteria, extracted the data, assessed the methodological quality of the included studies, and conducted meta-analysis.

Results: A total of 2486 patients from 19 studies were included. PTEN expression was significantly correlated with gender, smoking history, histology (adenocarcinoma [ADC] vs. squamous cell carcinoma), tumor node metastasis stage (I–II vs. III–IV), N status (N0 vs. N1–N3), and distant metastasis (M0 vs. M1). Loss of PTEN expression was associated with poorer overall survival, but had no significant association with disease-free survival. Subgroup analysis showed that negative PTEN expression was associated with a poorer outcome in Asian and ADC patients, but not in Western or squamous cell carcinoma patients.

Conclusion: Loss of PTEN might play an unfavorable prognostic role for overall survival of non-small cell lung cancer patients, especially Asian or ADC patients.

Introduction

Lung cancer is the main cause of cancer-related death around the world, with about 1.4 million deaths worldwide each year. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancer cases.1 Although some advances have been achieved in treatments, lung cancer has an extremely poor prognosis, with a five-year overall survival (OS) of 16% in the United States and less than 10% in the United Kingdom.2 Alone or in combination, the prognostic factors are variable measured indicators of individual patients, which may explain part of the population heterogeneity and provide information on clinical outcomes at the time of diagnosis. The tumor node metastasis (TNM) stage is thought to have an effect on survival in NSCLC patients; however, problems such as similar prognoses for patients with the same tumor stage have been indicated. Recent research has revealed that some biological markers may have an impact on survival in NSCLC patients.3–5

Phosphatase and tensin homolog (PTEN), also known as mutated in multiple advanced cancer 1 (MMAC1) or TGF-β-regulated and epithelial cell-enriched phosphatase 1 (TEP1), is a 47 kDa dual specific protein-phospholipid phosphatase, which was first identified as a tumor suppressor gene located at chromosome 10q23.3 by three separate groups of investigators in 1997.6–8 PTEN is an important negative regulator of the protein kinase B/phosphatidylinositols 3-kinase (PI3K) pathway, which is one of the most important pathways for cell growth, proliferation, and survival, by dephosphorylating phosphatidylinositol 3,4,5-triphosphate (PIP3) at its D3 position.9–12 It has also been suggested that PTEN regulates focal adhesion structure and
cell invasion and migration by controlling focal adhesion kinase (FAK) activity. In addition, PTEN can restrict cellular differentiation by decreasing the activation of mitogen-activated protein kinase (MAPK). PTEN may also inhibit angiogenesis by downregulating both hypoxia-inducible factor-1 alpha (HIF-1 alpha) and vascular endothelial growth factor (VEGF) in tumor cells. Recently, many studies have indicated that PTEN is related to survival in patients with malignant tumors, including esophageal squamous cell carcinoma, acute myeloid leukemia, and breast, prostate, and gastric cancers. However, the results relating to the prognostic role of PTEN expression in NSCLC are inconsistent among clinical studies; therefore, a systematic review and meta-analysis based on the published literature is necessary to provide further insights into this conflicting issue.

The aim of our study was to identify the prognostic value of PTEN expression in NSCLC patients. We also investigated the correlation between PTEN expression and clinicopathological characteristics.

**Methods**

This systematic review and meta-analysis was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement protocol.

**Search strategy**

We searched MEDLINE (via PubMed), Embase (via OVID), CENTRAL (via the Cochrane Library), and the Chinese BioMedical Literature Database (CBM) to October 2016 to identify studies relevant to this review. Our search strategy included the following subject headings and/or keywords variably combined by “lung neoplasm,” “PTEN,” and “prognosis.” The detailed PubMed search strategy is shown in Figure 1. In addition, reference lists of the articles initially detected were searched manually to identify additional relevant reports. The eligibility of references retrieved by the search was assessed independently by two of the authors, and the review authors resolved differences of opinion by discussion or by appeal to a third review author when necessary. The full text of the remaining articles, including the references, was examined to determine whether the articles contained relevant information.

**Inclusion and exclusion criteria**

Studies were considered eligible if they met all of the following inclusion criteria: (i) the study population consisted of primary NSCLC patients; (ii) PTEN expression was evaluated in primary lung carcinoma tissues by immunohistochemistry (IHC), reverse-transcriptase (RT)-PCR, or fluorescence in situ hybridization (FISH); and (iii) the association between PTEN expression and OS and disease-free survival (DFS) were measured and/or the associations of PTEN expression and clinical characteristics was reported. Studies were excluded based on any of the following criteria: (i) reviews, letters, laboratory research, and animal experiments were excluded based on any of the following criteria: (i) reviews, letters, laboratory research, and animal experiments were excluded; (ii) the language was not English or Chinese; or (iii) the study lacked critical data for hazard ratio (HR) analysis.

**Quality assessment**

Quality assessment of individual studies was performed independently by two of the authors, using the Newcastle–Ottawa Scale (NOS) for cohort studies. The scale allocates stars (maximum of 9) for quality of selection, comparability, and outcome of study participants. NOS scores of >6 were defined as high-quality studies. Any discrepancies were addressed by joint reevaluation of the original article.

**Data extraction**

Data were extracted from the selected studies independently by two of the authors, using a predefined standardized form and disagreements were resolved by discussion between two review authors or by appealing to a third review author. The original data included PTEN expression, Kaplan–Meier (K–M) survival curves, or HR and 95% confidence interval (CI) of survival outcomes. Multivariate Cox hazard regression analysis data was our priority, but if not obtained, univariate Cox hazard regression analysis or K–M survival curves with log-rank P value of survival outcomes were used instead. Because HRs were not available in all of the included studies, we calculated...
the HR with 95% CI using survival rates, enrolled samples, and corresponding P values from log-rank test in accordance with the described instructions. The relevant formulas are as follows:

\[
O - E = \sqrt{\frac{\text{Total observed events} \times \text{Analyzed research} \times \text{Analyzed control}}{\text{(Analyzed research + Analyzed control)}}} 
\times (Z \text{ score for } P \text{ value}/2)
\]

\[
V = \frac{\text{Total observed events} \times \text{Analyzed research} \times \text{Analyzed control}}{\left(\text{Analyzed research + Analyzed control}\right)^2}
\]

\[
HR = \text{Exp}\left(- \frac{O - E}{V}\right)
\]

where \(O - E\) is the log rank Observed minus Expected events and \(V\) is the log rank Variance.\(^{26}\) We then extracted the associated details by Engauge Digitizer 4.1 (http://sourceforge.net) from the K-M curves to measure the accuracy of estimated HRs. We extracted basic characteristics, including first author (year), primary treatment, country, study period, study design, number of patients, number of patients with evaluated PTEN expression and/or survival data, stage, method, cut-off/scoring categories, antibody, median follow-up, patients’ average age when diagnosed with lung cancer, histology, and attitude conclusion from eligible articles.

**Statistical analysis**

The log HR was chosen as the appropriate summary statistic because it was the only summary statistic that allowed for both censoring and time to an event.\(^{27}\) However, these relevant statistical variables were not explicitly provided in most studies; therefore, we extracted associated data from K–M survival curves. We carried out meta-analysis on PTEN expression in NSCLC cells for OS and DFS. We also analyzed correlations between PTEN expression and clinical characteristics, including age, gender, grade, smoking history, histology, primary tumor (pT) stage, TNM stage, lymph node metastasis, and other characteristics. According to clinical characteristics, stages I and II, stages III and IV, T2, T3, and T4 were combined, while well-differentiated (G1) and moderately differentiated (G2) were combined and poorly differentiated (G3) was separated. Their correlations were described by odds ratio (OR). The effects of PTEN expression on survival outcome (OS/DFS) and correlations between PTEN expression and clinical characteristics were estimated by forest plots. Heterogeneity was defined as \(P < 0.10\) or \(I^2 > 50\%\). When homogeneity was good (\(P > 0.10\), \(I^2 < 50\%\)), a fixed effect model was used to combine effective sizes, otherwise a random effect model was used. Subgroup analyses were performed to investigate the potential causes of heterogeneity according to region, sample size, follow-up period, test methods, and NOS scores. Meta-regression was also used to identify the source of heterogeneity. An observed HR > 1 indicated a worse outcome for the positive group compared with the negative group and was considered significant if the 95% CI did not overlap 1. The potential publication bias was evaluated by Begg’s rank correlation and Egger’s test, with \(P > 0.05\) indicating no potential publication bias.\(^{28}\) Meta-analysis and publication biases were both performed by STATA 13.0 (STATA Corporation, College Station, TX, USA).

**Results**

**Reference retrieval**

After primary retrieval, a total of 231 potentially relevant studies were initially incorporated into our study, including 121 from MEDLINE, 89 from Embase, 17 from CBM, 1 from CENTRAL, and 3 from reference lists. Forty were excluded as duplicates and 151 were excluded by title/abstract screening. Full texts were retrieved for the remaining 40 studies. Nineteen retrospective trials finally met all of the criteria for inclusion in the analysis, which included 3071 patients with a median number of 161.6 patients per study (Fig 2).

**Characteristics and qualities of the included studies**

The clinical characteristics of the patients are listed in Table 1. All of the studies were published after 2005. Only one study was a multinational study undertaken in 30 different countries, while the other 18 studies were single-center studies (14 in Asian countries and 4 in Western countries).\(^{39}\) NSCLC trials included either all histological subtypes\(^{29,33,35–41,43–47}\) (\(n = 17\)), or adenocarcinoma (ADC) (\(n = 2\)).\(^{34,42}\) Data related to local advanced disease (stages I–III) comprised three of the 19 NSCLC trials,\(^{32,36,42}\) while
13 studies dealt with any stage (I–IV). Shin et al. assessed local early disease stage (I). O’Byrne et al. only involved patients with stages III–IV disease and the patients were separated into two groups according to different treatments (chemotherapy and chemotherapy + cetuximab). In Lim et al.’s study, patients were divided into two groups on the basis of different stage and treatment (stage I treated with surgery and stage IV treated with gefitinib).

Quality assessments of individual studies are shown in Table S1. We used the NOS for cohort studies to assess included studies, which included three aspects (selection, comparability, and outcome) and eight items. All studies scored either six or seven.

**Correlation between phosphatase and tensin homolog (PTEN) expression and clinicopathological characteristics**

The studies that referred to a correlation between PTEN expression and clinical characteristics were gathered to evaluate the combined ORs. We found that PTEN
| Study (year) | Country | Study period | Study design | NOS | N | n | Primary treatment | Stage | Histology | Cut-off/scoring categories | Antibody | Follow-up (months) | Age (years) | Survival Outcome | Attitude |
|-------------|---------|--------------|--------------|-----|---|---|--------------------|-------|-----------|--------------------------|-----------|------------------|-----------|------------------|---------|
| Wang et al. 2015 | China | 2004–2010 | ROS | 7 | 92 | 92 | Surgery | I–IV | ADC | Monoclonal, mouse anti-human PTEN | Scoring = 2 | 32 | 23–83 | OS | Positive |
| Shin et al. 2015 | Korea | 2000–2005 | ROS | 6 | 408 | 250 | Surgery | | | NR | Scoring = 1 | 15.8 | 64 | OS | Positive |
| Li et al. 2015 | China | 2004–2006 | ROS | 6 | 68 | 68 | Surgery | | | Monoclonal, rabbit anti-human PTEN | Scoring = 2 | 32 | 74% | IHC | Positive |
| Ji et al. 2014 | China | 2007–2008 | ROS | 6 | 67 | 67 | Surgery | | | Monoclonal, mouse anti-human PTEN | Scoring = 5 | 31 | 28–80 | OS | Positive |
| Yoo et al. 2013 | Korea | 2000–2005 | ROS | 6 | 408 | 250 | Surgery | | | NR | Scoring = 1 | NR | 62.1 | OS | Positive |
| Li et al. 2015 | China | 2004–2006 | ROS | 6 | 68 | 68 | Surgery | | | IHC | 74% | Monoclonal, rabbit anti-human PTEN | | 15.8 | 64 | OS | Positive |
| Ji et al. 2014 | China | 2007–2008 | ROS | 6 | 67 | 67 | Surgery | | | IHC | Scoring = 2 | Monoclonal, mouse anti-human PTEN | | 31 | 28–80 | OS | Positive |
| Yoo et al. 2013 | Korea | 2000–2005 | ROS | 6 | 408 | 250 | Surgery | | | NR | Scoring = 1 | NR | 62.1 | OS | Positive |
| Li et al. 2015 | China | 2004–2006 | ROS | 6 | 68 | 68 | Surgery | | | IHC | 50% | Monoclonal, rabbit anti-human PTEN | | 31 | 28–80 | OS | Positive |
| Ji et al. 2014 | China | 2007–2008 | ROS | 6 | 67 | 67 | Surgery | | | IHC | Scoring = 2 | Monoclonal, mouse anti-human PTEN | | 31 | 28–80 | OS | Positive |
| Yoo et al. 2013 | Korea | 2000–2005 | ROS | 6 | 408 | 250 | Surgery | | | NR | Scoring = 1 | NR | 62.1 | OS | Positive |
| Li et al. 2015 | China | 2004–2006 | ROS | 6 | 68 | 68 | Surgery | | | IHC | 50% | Monoclonal, rabbit anti-human PTEN | | 31 | 28–80 | OS | Positive |
| Ji et al. 2014 | China | 2007–2008 | ROS | 6 | 67 | 67 | Surgery | | | IHC | Scoring = 2 | Monoclonal, mouse anti-human PTEN | | 31 | 28–80 | OS | Positive |
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| Yoo et al. 2013 | Korea | 2000–2005 | ROS | 6 | 408 | 250 | Surgery | | | NR | Scoring = 1 | NR | 62.1 | OS | Positive |
| Li et al. 2015 | China | 2004–2006 | ROS | 6 | 68 | 68 | Surgery | | | IHC | 50% | Monoclonal, rabbit anti-human PTEN | | 31 | 28–80 | OS | Positive |
| Ji et al. 2014 | China | 2007–2008 | ROS | 6 | 67 | 67 | Surgery | | | IHC | Scoring = 2 | Monoclonal, mouse anti-human PTEN | | 31 | 28–80 | OS | Positive |

†Patients treated with chemotherapy. ††Patients treated with chemotherapy + cetuximab. ADC, adenocarcinoma; Cet, cetuximab; CT, chemotherapy; DFS, disease-free survival; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; N, number of patients included in the study; n, number of tests of PTEN to analyze survival outcome; NR, no referred; NOS, Newcastle-Ottawa Scale; OS, overall survival; PTEN, phosphatase and tensin homolog; ROS, retrospective observational study; RT, reverse transcription; SCC, squamous cell carcinoma.
expression was significantly correlated with gender (male vs. female: OR 0.59, 95% CI 0.47–0.75; P = 0.000), smoking history (yes vs. no: OR 2.22, 95% CI 1.57–3.14; P = 0.000), histology (ADC vs. squamous cell carcinoma [SCC]: OR 1.53, 95% CI 1.03–2.29; P = 0.037), TNM stage (I–II vs. III–IV: OR 1.96, 95% CI 1.13–3.40; P = 0.017), N status (N0 vs. N1–N3: OR 2.22, 95% CI 1.31–3.76; P = 0.003), and distant metastasis (M0 vs. M1: OR 6.47, 95% CI 2.19–19.14; P = 0.001) (Table 2).

**Correlation between PTEN expression and survival outcomes**

All articles, including 2486 patients, listed the relationship between PTEN expression and survival outcome in NSCLC.29–47 The combined HR was 0.51 (95% CI 0.42–0.62; P = 0.000, I² = 59.5%) for OS in 16 studies (Fig 3),29–32,36–47 but was 0.82 (95% CI 0.26–2.60; P = 0.733, I² = 84.7%) for DFS in three studies (Fig 4; Table 3).33–35 Negative PTEN expression was a predictor of poor OS (but not DFS) in NSCLC patients. We also conducted subgroup analysis according to region, sample size, follow-up period, test methods, and NOS scores (Table 4). Interestingly, we found that the patients with positive PTEN tended to have favorable OS in Asian countries (HR 0.46, 95% CI 0.40–0.53; P = 0.027) compared with Western countries (HR 0.82, 95% CI 0.52–1.30; P = 0.319). Four trials for ADC and three for SCC were assessable for OS (Fig 3, Table 3). The combined HR for OS in ADC (95% CI) was 0.61 (0.44, 0.85; I² = 0.0%, P = 0.003); however, the combined HR for OS in SCC (95% CI) was 0.78 (0.54, 1.12; I² = 40.7%, P = 0.178). Moderate heterogeneity was found in the meta-analysis for HR (OS) of the prognostic role of PTEN expression. Univariable meta-regression was used to identify the source of heterogeneity, and we found that different regions (Asian vs. Western countries) could explain 53.1% of the heterogeneity (P = 0.039), which is consistent with the earlier result in OS subgroup analysis. However, published year (P = 0.942), NOS score (P = 0.506), and TNM stage (P = 0.388) could not explain the heterogeneity.

**Assessment of publication bias**

Publication bias is a major concern for all forms of meta-analyses, because positive results tend to be accepted by journals while negative results are often rejected or are not even submitted. Two methods, including Begg’s funnel plot and Egger’s test, were used to evaluate publication bias of the meta-analysis. No publication bias of the prognostic value of PTEN for OS in NSCLC was discovered (Fig 5). Both the Begg’s test (P = 0.112) and the Egger’s test (P = 0.272) found little publication bias. Although little publication bias was detected in our study, we caution the poor sensitivity of Begg’s and Egger’s tests when the number of eligible articles is fewer than 20.

**Discussion**

Phosphatase and tensin homolog, regarded as a tumor suppressor gene, regulates many cellular processes, including proliferation, survival, energy metabolism, cellular architecture, and motility.48 PTEN inactivation is frequently found in many tumors, including lung, endometrial, bladder, renal, and breast cancers.49 We found that PTEN expression was markedly lower in patients with certain clinicopathological characteristics, including men, SCC (vs. ADC), late N status (N1–N3), distant metastasis, and late TNM stage (stage III–IV), which implied that a loss of PTEN expression tended to occur in late NSCLC stage and indicated a poor prognosis. No association was found between PTEN expression and age, grade, or primary tumor stage.
Figure 3 Pooled hazard ratios (HRs) for assessing the prognostic value of phosphatase and tensin homolog expression for overall survival in (a) non-small cell lung cancer, (b) adenocarcinoma, and (c) squamous cell carcinoma. † Patients treated with chemotherapy; ‡ patients treated with chemotherapy + cetuximab. CI, confidence interval; D+L, DerSimonian & Laird; I−V, inverse variance.

| Study ID | HR (95% CI) | Weight (I−V) |
|----------|-------------|--------------|
| Asian Country | | |
| Hu et al. (2012) | 0.17 (0.09, 0.33) | 3.03 |
| Endoh et al. (2006) | 0.11 (0.01, 1.18) | 0.23 |
| Zheng et al. (2007) | 0.55 (0.34, 0.87) | 5.91 |
| Tang et al. (2006) | 0.37 (0.22, 0.64) | 4.57 |
| Lim et al. (2007) | 0.26 (0.07, 0.95) | 0.77 |
| Shin et al. (2015) | 0.61 (0.39, 0.93) | 6.90 |
| Kim et al. et al. (2012) | 0.73 (0.48, 1.11) | 7.42 |
| Ji et al. (2014) | 0.35 (0.24, 0.76) | 3.92 |
| Wang et al. (2009) | 0.47 (0.38, 0.59) | 27.92 |
| Kim et al. et al. (2009) | 0.52 (0.25, 1.10) | 7.37 |
| Wang et al. (2015) | 0.28 (0.16, 0.48) | 4.21 |
| Li et al. et al. (2015) | 0.57 (0.33, 0.98) | 4.40 |
| An et al. (2012) | 0.40 (0.19, 0.82) | 2.51 |
| I−V Subtotal (I−squared = 48.1%, P = 0.027) | 0.46 (0.40, 0.53) | 74.16 |

| Multi-Country | | |
| O’Byrne et al. (2011) | 0.80 (0.55, 1.16) | 9.36 |
| O’Byrne et al. (2011) | 0.77 (0.54, 1.10) | 10.30 |
| I−V Subtotal (I−squared = 0.0%, P = 0.884) | 0.78 (0.61, 1.01) | 19.66 |

| Western Country | | |
| Regina et al. (2009) | 0.67 (0.29, 1.57) | 1.83 |
| Zolota et al. (2010) | 0.44 (0.14, 1.34) | 1.02 |
| Yoshizawa et al. (2010) | 1.11 (0.63, 2.20) | 3.33 |
| I−V Subtotal (I−squared = 12.6%, P = 0.319) | 0.82 (0.52, 1.30) | 6.18 |

Heterogeneity between groups: P = 0.000
I−V Overall (I−squared = 59.5%, P = 0.001) 0.53 (0.47, 0.60) 100.00
D+L Overall 0.51 (0.42, 0.62) 0.54

| Study ID | HR (95% CI) | Weight |
|----------|-------------|--------|
| Shin et al. (2015) | 0.61 (0.39, 0.93) | 56.31 |
| Li et al. (2015) | 0.68 (0.24, 1.97) | 9.60 |
| Yoshizawa et al. (2010) | 0.72 (0.34, 1.66) | 14.73 |
| Kim et al. (2012) | 0.52 (0.25, 1.10) | 19.36 |
| Overall (I−squared = 0.0%, P = 0.949) | 0.61 (0.44, 0.85) | 100.00 |

| Study ID | HR (95% CI) | Weight |
|----------|-------------|--------|
| Yoshizawa et al. (2010) | 1.61 (0.71, 4.64) | 14.91 |
| Kim et al. (2012) | 0.73 (0.48, 1.11) | 74.78 |
| Zolota et al. (2010) | 0.44 (0.14, 1.34) | 10.30 |
| Overall (I−squared = 40.7%, P = 0.185) | 0.78 (0.54, 1.12) | 100.00 |
In the present meta-analysis, we combined 19 published studies including 2486 patients with NSCLC to yield summary statistics, which indicate that negative expression of PTEN has a significant correlation with poorer OS in NSCLC; however, it is not an unfavorable prognostic factor for DFS in NSCLC patients. In subgroup analysis, we found that loss of PTEN expression only predicted adverse clinical outcomes in ADC patients. Interestingly, when we investigated survival by different regions, the poorer OS associated with PTEN loss was only observed in Asian countries.

Table 3: Meta-analyses of PTEN expression to predict survival outcome in NSCLC patients

| Tumor type | Outcome | N | Patients | Heterogeneity (I², P) | Model | HR (95% CI) | P | Conclusion |
|------------|---------|---|----------|-----------------------|-------|-------------|---|------------|
| NSCLC      | OS      | 16| 2181     | 59.5%, 0.001          | Random| 0.53 (0.47,0.60) | 0.000 | Positive   |
| ADC        | OS      | 4 | 504      | 4.0%, 0.949           | Fixed | 0.61 (0.44,0.85) | 0.003 | Positive   |
| SCC        | OS      | 3 | 321      | 40.7%, 0.185          | Fixed | 0.78 (0.54,1.12) | 0.000 | Negative   |

ADC, adenocarcinoma; CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; NSCLC, non-small cell lung cancer; N, reference count; OS, overall survival; PTEN, phosphatase and tensin homolog; SCC, squamous cell carcinoma.

Table 4: Subgroup analyses of the relationships between PTEN expression and overall survival

| Comparison variables | Number of studies (I² statistics %) | HR (95% CI), P | Heterogeneity between sub-groups (P) |
|----------------------|------------------------------------|----------------|-------------------------------------|
| Total                | 16 (59.5%)                         | 0.51 (0.42–0.62), 0.000 | NA                                 |
| Regions              |                                    |                |                                     |
| Asian countries      | 12 (48.1%)                         | 0.49 (0.40–0.53), 0.000 | 0.000                              |
| Western countries    | 3 (12.6%)                          | 0.82 (0.52–1.30), 0.399 |                                     |
| Multi-countries      | 1 (NA)                             | 0.78 (0.61–1.01), 0.064 |                                     |
| Sample size          |                                    |                |                                     |
| >100                 | 8 (69.7%)                          | 0.57 (0.50–0.64), 0.000 | 0.017                              |
| ≤100                 | 8 (0.0%)                           | 0.40 (0.31–0.52), 0.000 |                                     |
| Follow-up period     |                                    |                |                                     |
| Referred             | 7 (74.3%)                          | 0.56 (0.46–0.67), 0.000 | 0.565                              |
| Not referred         | 9 (37.6%)                          | 0.52 (0.45–0.60), 0.000 |                                     |
| Test method          |                                    |                |                                     |
| IHC                  | 13 (55%)                           | 0.48 (0.42–0.55), 0.000 | 0.001                              |
| Others               | 3 (0%)                             | 0.76 (0.59–0.97), 0.027 |                                     |
| NOS score            |                                    |                |                                     |
| ≤6                   | 10 (59.2%)                         | 0.48 (0.41–0.56), 0.000 | 0.053                              |
| >6                   | 6 (56.6%)                          | 0.60 (0.51–0.71), 0.000 |                                     |

CI, confidence interval; HR, hazard ratio; ICH, immunohistochemistry; NA, not applicable; NOS, Newcastle–Ottawa Scale; PTEN, phosphatase and tensin homolog.
patients. Thus, our results suggest that loss of PTEN expression was a more appropriate prognostic marker for ADC or Asian patients than for SCC or Western patients. However, further studies are required to address this issue.

Our study has several limitations. First, the findings of a meta-analysis depend on the quality of the individual studies, as their potential problems and biases may affect the pooled data. According to the NOS quality assessment performed, 10 of the 16 involved studies scored six, and the other six scored seven, which indicated moderate quality of all of the studies. Second, the method of HR extrapolation is potentially biased. If the authors did not report the required statistics, we calculated them from the data available in the article; if this was not possible, we extrapolated them from the survival curves; therefore some subjective data may affect the final conclusion. Third, we did not search unpublished and grey literature databases, which may lead to potential publication bias. Furthermore, there is also a language bias, as we only screened English and Chinese literature.

In conclusion, this meta-analysis implied that a loss of PTEN expression, which is associated with gender, smoking history, histology, TNM stage, N status, and distant metastasis, might play an unfavorable prognostic role for overall survival in NSCLC patients, especially Asian or ADC patients. However, there is moderate heterogeneity between the studies and further rigorous and high-quality investigation of the effectiveness of PTEN as a therapeutic target for NSCLC is warranted.

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Disclosure

No authors report any conflict of interest.

References

1. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. (Published erratum appears in CA Cancer J Clin 2011; 61: 134.) CA Cancer J Clin 2011; 61: 69–90.
2. Bunn PA Jr. Worldwide overview of the current status of lung cancer diagnosis and treatment. Arch Pathol Lab Med 2012; 136: 1478–81.
3. Yang Y, Xie Y, Xian L. Breast cancer susceptibility gene 1 (BRCA1) predict clinical outcome in platinum- and toxal-based chemotherapy in non-small-cell lung cancer (NSCLC) patients: A system review and meta-analysis. J Exp Clin Cancer Res 2013; 32: 15.
4. Zhang T, Zhang DM, Zhao D et al. The prognostic value of osteopontin expression in non-small cell lung cancer: A meta-analysis. J Mol Histol 2014; 45: 533–40.
5. Liang Y, Guo S, Zhou Q. Prognostic value of matrix metalloproteinase-7 expression in patients with non-small cell lung cancer. Tumour Biol 2014; 35: 3717–24.
6. Steck PA, Pershouse MA, Jasser SA et al. Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers. Nat Genet 1997; 15: 356–62.
7. Li DM, Sun H. TEP1, encoded by a candidate tumor suppressor locus, is a novel protein tyrosine phosphatase regulated by transforming growth factor beta. Cancer Res 1997; 57: 2124–9.
8. Li J, Yen C, Liaw D et al. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science 1997; 275: 1943–7.
9. Stambolic V, Suzuki A, de la Pompa JL et al. Negative regulation of PKB/Akt-dependent cell survival by the tumor suppressor PTEN. Cell 1998; 95: 29–39.
10. Cully M, You H, Levine AJ, Mak TW. Beyond PTEN mutations: The PI3K pathway as an integrator of multiple inputs during tumorigenesis. Nat Rev Cancer 2006; 6: 184–92.
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11 Sun H, Lesche R, Li DM et al. PTEN modulates cell cycle progression and cell survival by regulating phosphatidylinositol 3,4,5-trisphosphate and Akt/protein kinase B signaling pathway. Proc Natl Acad Sci U S A 1999; 96: 6199–204.

12 Wu X, Senechal K, Neshat MS, Whang YE, Sawyers CL. The PTEN/MMAC1 tumor suppressor phosphatase functions as a negative regulator of the phosphoinositide 3-kinase/Akt pathway. Proc Natl Acad Sci U S A 1998; 95: 15587–91.

13 Tamura M, Gu J, Matsumoto K, Aota S, Parsons R, Yamada KM. Inhibition of cell migration, spreading, and focal adhesions by tumor suppressor PTEN. Science 1998; 280: 1614–7.

14 Tamura M, Gu J, Danen EH, Takino T, Miyamoto S, Yamada KM. PTEN interactions with focal adhesion kinase and suppression of the extracellular matrix-dependent phosphatidylinositol 3-kinase/Akt cell survival pathway. J Biol Chem 1999; 274: 20693–703.

15 Weng LP, Smith WM, Brown JL, Eng C. PTEN inhibits insulin-stimulated MEK/ERK activation and cell growth by blocking IRS-1 phosphorylation and IRS-1/Grb-2/Sos complex formation in a breast cancer model. Hum Mol Genet 2001; 10: 605–16.

16 Yart A, Laffargue M, Mayeux P et al. A critical role for phosphoinositide 3-kinase upstream of Gab1 and SHP2 in the activation of ras and mitogen-activated protein kinases by epidermal growth factor. J Biol Chem 2001; 276: 8856–64.

17 Zundel W, Schindler C, Haas-Kogan D et al. Loss of PTEN facilitates HIF-1-mediated gene expression. Genes Dev 2000; 14: 391–6.

18 Gomez-Manzano C, Fuelo J, Jiang H et al. Mechanisms underlying PTEN regulation of vascular endothelial growth factor and angiogenesis. Ann Neurol 2003; 53: 109–17.

19 Lu J, Pan Y, Xia X, Gu Y, Lei Y. Prognostic significance of mTOR and PTEN in patients with esophageal squamous cell carcinoma. Biomed Res Int 2015; 2015: 417210.

20 Huang X, Li D, Li T, Zhao BO, Chen X. Prognostic value of PTEN and Ki67 expression in NSCLC patients with PTEN, p-EGFR and p-Akt de

21 Beg S, Siraj AK, Prabhakaran S et al. Loss of PTEN expression is associated with aggressive behavior and poor prognosis in Middle Eastern triple-negative breast cancer. Breast Cancer Res Treat 2015; 151: 541–53.

22 Kluth M, Runte F, Barow P et al. Concurrent deletion of 16q23 and PTEN is an independent prognostic feature in prostate cancer. Int J Cancer 2015; 137: 2354–63.

23 Li Y, Cai J, Zhang CH et al. High-expression of DJ-1 and loss of PTEN associated with tumor metastasis and correlated with poor prognosis of gastric carcinoma. Int J Med Sci 2013; 10: 1689–97.

24 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. (Published erratum appears in Int J Surg 2010; 8: 658.) Int J Surg 2010; 8: 336–41.

25 Wells GA, Shea B, O’Connell D et al. The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses. 2008. [Cited 18 Feb 2017.] Available from URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

26 Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials 2007; 8: 16.

27 Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. (Published erratum appears in Stat Med 2004; 23: 1817.) Stat Med 1998; 17: 2815–34.

28 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088–101.

29 Wang J, Chen H, Liao Y et al. Expression and clinical evidence of miR-494 and PTEN in non-small cell lung cancer. Tumour Biol 2015; 36: 6965–72.

30 Shin E, Choi CM, Kim HR, Jang SJ, Park YS. Immunohistochemical characterization of the mTOR pathway in stage-I non-small-cell lung carcinoma. Lung Cancer 2015; 89: 13–8.

31 Li XB, Yang Y, Zhang HQ et al. High levels of phosphatase and tensin homolog expression predict favorable prognosis in patients with non-small cell lung cancer. Eur Rev Med Pharmacol Sci 2015; 19: 2231–9.

32 Ji Y, Zheng M, Ye S, Chen J, Chen Y. PTEN and Ki67 expression is associated with clinicopathologic features of non-small cell lung cancer. J Biomed Res 2014; 28: 462–7.

33 Yoo SB, Kim YJ, Kim H et al. Alteration of the E-cadherin/beta-catenin complex predicts poor response to epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR-TKI) treatment. Ann Surg Oncol 2013; 20 (Suppl. 3): S545–52.

34 Yanagawa N, Leduc C, Kohler D et al. Loss of phosphatase and tensin homolog protein expression is an independent poor prognostic marker in lung adenocarcinoma. J Thorac Oncol 2012; 7: 1513–21.

35 Wang L, Yue W, Zhang L, Zhao X, Wang Y, Xu S. mTOR and PTEN expression in non-small cell lung cancer: Analysis by real-time fluorescence quantitative polymerase chain reaction and immunohistochemistry. Surg Today 2012; 42: 419–25.

36 Kim HS, Kim GY, Lim SJ, Kim YW. Expression of the mammalian target of rapamycin pathway markers in lung adenocarcinoma and squamous cell carcinoma. Pathobiology 2012; 79: 84–93.

37 Hu J, Liu YL, Piao SL, Yang DD, Yang YM, Cai L. Expression patterns of USP22 and potential targets BMI-1, PTEN, p-AKT in non-small-cell lung cancer. Lung Cancer 2012; 77: 593–9.

38 An SJ, Lin QX, Chen ZH et al. Combinations of laminin 5 with PTEN, p-EGFR and p-Akt define a group of distinct molecular subsets indicative of poor prognosis in patients with non-small cell lung cancer. Exp Ther Med 2012; 4: 226–30.
39 O’Byrne KJ, Gatzemeier U, Bondarenko I et al. Molecular biomarkers in non-small-cell lung cancer: A retrospective analysis of data from the phase 3 FLEX study. Lancet Oncol 2011; 12: 795–805.

40 Zolota VG, Tzelepi VN, Leotsinidis M et al. Histologic-type specific role of cell cycle regulators in non-small cell lung carcinoma. J Surg Res 2010; 164: 256–65.

41 Yoshizawa A, Fukuoka J, Shimizu S et al. Overexpression of phospho-eIF4E is associated with survival through AKT pathway in non-small cell lung cancer. Clin Cancer Res 2010; 16: 240–8.

42 Wang C, Yang R, Yue D, Zhang Z. Expression of FAK and PTEN in bronchioloalveolar carcinoma and lung adenocarcinoma. Lung 2009; 187: 104–9.

43 Regina S, Valentin JB, Lachot S, Lemarié E, Rollin J, Gruel Y. Increased tissue factor expression is associated with reduced survival in non-small cell lung cancer and with mutations of TP53 and PTEN. Clin Chem 2009; 55: 1834–42.

44 Zheng H, Tsucheyama K, Takahashi H et al. Expression of PTEN and FHIT is involved in regulating the balance between apoptosis and proliferation in lung carcinomas. Anticancer Res 2007; 27: 575–81.

45 Lim WT, Zhang WH, Miller CR et al. PTEN and phosphorylated AKT expression and prognosis in early- and late-stage non-small cell lung cancer. Oncol Rep 2007; 17: 853–7.

46 Tang JM, He QY, Guo RX, Chang XJ. Phosphorylated Akt overexpression and loss of PTEN expression in non-small cell lung cancer confers poor prognosis. Lung Cancer 2006; 51: 181–91.

47 Endoh H, Yatabe Y, Kosaka T, Kuwano H, Mitsudomi T. PTEN and PIK3CA expression is associated with prolonged survival after gefitinib treatment in EGFR-mutated lung cancer patients. J Thorac Oncol 2006; 1: 629–34.

48 Worby CA, Dixon JE. PTEN. Annu Rev Biochem 2014; 83: 641–69.

49 Yin Y, Shen WH. PTEN: A new guardian of the genome. Oncogene 2008; 27: 5443–53.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

Table S1 Quality assessment of individual studies using the Newcastle-Ottawa Scale for cohort studies