The Role of the PTEN/PI3K/Akt Pathway on Prognosis in Epithelial Ovarian Cancer: A Meta-Analysis

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. PTEN/PI3K/Akt • Overall survival • Progression-free survival • Epithelial ovarian cancer • Meta-analysis

ABSTRACT

Introduction. The PTEN/PI3K/Akt signaling pathway, a key player in mediating apoptosis, metabolism, cell proliferation, and cell growth, is frequently dysregulated in many cancers. However, the pathway's prognostic impact in epithelial ovarian cancer (EOC) is still inconsistent. We performed a meta-analysis based on individual study outcomes to more precisely evaluate its clinical significance in EOC patients.

Methods. We searched all potentially relevant studies published between January 1, 1990, and March 1, 2013, that assessed the association between PTEN, PI3K, and Akt status and survival in EOC. Meta-analysis was performed using a fixed-effect or random-effects model as appropriate. We investigated the possibility of publication bias through a funnel plot and identified the heterogeneity by I^2 statistics.

Results. Eleven eligible studies were analyzed for PTEN, 5 for PI3K, and 11 for pAkt. High PI3K and pAkt expression was associated with poor overall survival (OS; pooled adjusted hazard ratio [HR] = 1.44, 95% CI, 1.08–1.91 for PI3K; HR = 1.60, 95% CI, 1.26–2.04 for pAkt). In addition, both the meta-analyses of univariate and multivariate estimates showed that only high pAkt expression was significantly associated with poor progression-free survival (PFS; pooled unadjusted HR = 1.24, 95% CI, 1.10–1.39; pooled adjusted HR = 1.65, 95% CI, 1.07–2.55).

Conclusion. Published studies suggest that high pAkt expression is significantly associated with poor OS and PFS in EOC patients, but currently available evidence is insufficient to recommend that PTEN, PI3K, or Akt be used as prognostic predictors in EOC in clinical practice. *The Oncologist* 2014;19:528–535

Implications for Practice: We performed a meta-analysis based on individual study outcomes to evaluate the clinical significance of the PTEN/PI3K/Akt signaling pathway in epithelial ovarian cancer (EOC) patients. We found that high expression of activated Akt (pAkt) was significantly associated with poor survival in EOC patients, but currently available evidence is insufficient to recommend PTEN, PI3K, or Akt to be used as a prognostic predictor in EOC in clinical practice. This study is both important and immediately clinically relevant because currently, in spite of tremendous efforts in the field of biomarker discovery and development, for EOC, molecular assays in the clinicopathologic and prognosis toolbox are lacking. Furthermore, identification of more accurate and more effective detection techniques and unified evaluation criteria to mandate homogeneous data collection is urgently needed.

INTRODUCTION

Epithelial ovarian cancer (EOC) is the most frequent cause of death from gynecological malignancies among American women [1] and is characterized by a low rate of early diagnosis, high rate of metastasis, very poor prognosis, and lack of effective therapies. The current management of patients with advanced disease involves optimal surgical debulking followed by chemotherapy. Platinum-based regimens remain at the core of postoperative treatment. Overall tumor response rates initially associated with this treatment are relatively high and range from approximately 70% to 80% [2, 3]. However, long-term survival remains poor as a result of recurrence and resistance to chemotherapeutics. Current clinicopathologic prognostic factors do not allow

individualized prediction of disease outcome. Identification of molecular markers predicting the clinical outcomes would be of great value for adjustment of patients' treatment [4].

PTEN (phosphatase and tensin homolog deleted on chromosome 10) is a dual protein/lipid phosphatase that dephosphorylates the phosphatidylinositol 3-kinase, the product of PI3K [5] (Fig. 1). PTEN can suppress human ovarian cancer cell growth and provoke an arrest in G1 of the cell cycle through negatively regulating the PI3K/Akt (protein kinase B) pathway [6–8]. PI3K is a phosphatidylinositol kinase, including a regulatory subunit p85 and catalytic subunit p110, which is encoded by the PIK3CA gene. Akt is a cytoplasmic

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Figure 1. Overview of the PTEN/PI3K/Akt signaling pathway. PI3K is initially activated by membrane receptor (such as cytokine receptor, RTK, CD19, and integrin). An increase in PI3K function leads to the accumulation of PIP3, which subsequently activates PDK1 and Akt. PTEN regulates Akt by dephosphorylating PIP3, the product of PI3K. Increased Akt activity results in subsequent downstream functions.

Abbreviations: PDK1, pyruvate dehydrogenase kinase isozyme 1; PI3K, phosphoinositide 3-kinase; PIP2, phosphatidylinositol-4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-triphosphate; PTEN, phosphatase and tensin homolog deleted on chromosome 10; R, cell surface receptor.

serine-threonine protein kinase that promotes cell cycle progression and inhibits apoptosis when activated (phosphorylation of the protein at T308 and S473 [pAkt]) [9]. Several studies have shown that abnormal expression of the PTEN/PI3K/Akt pathway has been associated with poor prognosis in ovarian carcinomas [10–12]. However, the results from the previous studies are inconclusive. In order to more precisely evaluate the clinical significance of the PTEN/PI3K/Akt pathway in EOC patients, we performed a meta-analysis based on individual study outcomes.

MATERIALS AND METHODS

We performed this meta-analysis according to the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines [13].

Search Strategy and Selection

All potentially relevant papers published in English between January 1, 1990, and March 1, 2013, were identified by searching PubMed using “ovarian cancer,” “PTEN,” “PI3K,” and “pAkt” as the search terms (Fig. 2). The reference lists of relevant reviews and all eligible articles were hand-searched to identify additional studies.

The studies were included if they met the following criteria: (a) an original paper on primary EOC, (b) a clinical study (prospective, randomized, retrospective, etc.) that investigated the association of PTEN, PI3K, and pAkt expression status with overall survival (OS) or progression-free survival (PFS) in EOC patients, (c) articles that presented a hazard ratio (HR) and 95% confidence interval (CI), (d) articles with enough data to assess the HR and 95% CI from univariate survival analysis, and

Figure 2. Process used for the trial selection.

(e) articles with all pathology specimens (such as tumor tissues) obtained at initial surgery prior to any therapeutics. The studies published in languages other than English were excluded from this meta-analysis, as were nonoriginal research articles, reviews, abstracts, and letters on nonepithelial or recurrent ovarian cancer. Furthermore, duplication of a previous publication and specimens collected after chemotherapy or radiotherapy were also excluded.

Figure 3. Funnel plot for publication bias showing the relationship between the effect size of individual studies and the precision of the study estimate for the PTEN/PI3K/Akt signaling pathway. **(A):** Hazard ratio for unadjusted overall survival. **(B):** Hazard ratio for adjusted overall survival. **(C):** Hazard ratio for unadjusted progression-free survival.

Abbreviations: PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog deleted on chromosome 10.

Data Extraction

In order to ensure homogeneity of the data gathering and to preclude subjectivity in the data collection and entry, two researchers independently extracted the data. Cases of disagreement were settled by iteration, discussion, and consensus. The following information was collected for each study: authors' names; year of publication; country; age of the patients at the time of diagnosis (mean, median, range); number of patients; study type (prospective, randomized, retrospective, etc.); time of follow-up (median, mean, minimum, and maximum); stage, tumor type, assay method, and scoring protocol used; treatment; number of biomarker-positive and -negative tumors; number of deaths (disease specific and overall); and results of univariate or multivariate survival analysis.

Assessment of Publication Bias and Statistical Analysis

The possibility of publication and selection bias was investigated using funnel plots and was tested by Egger's test [14, 15].

The HR was used as a measure of the prognostic value, which was defined as the risk of death for patients with biomarker-positive tumors over patients with biomarker-

negative tumors, so a $HR > 1$ indicated an increased risk of death in cases with biomarker-positive tumors. Using the methods described by Parmar et al. [16], we extracted a log-HR and its 95% CI from a univariate/multivariate survival analysis for each study. Subsequently, we calculated the pooled HRs and 95% CIs for prognosis using the DerSimonian-Laird random-effects or the Mantel-Haenszel fixed-effects model [17, 18]. In this meta-analysis, statistical heterogeneity among studies was assessed by the I^2 statistic [19], and an $I^2 > 50\%$ was considered as representing substantial heterogeneity between studies. Our meta-analyses were carried out by STATA, version 11 (Stata Corporation, College Station, TX, <http://www.stata.com>).

RESULTS

Study Characteristics

Of 20 eligible articles in this meta-analysis, there were 11 for PTEN, 5 for PI3K, and 11 for pAkt. The characteristics of studies analyzed are shown in supplemental online Table 1. The number of participants ranged from 17 to 522, and, in total, 2,499 patients were identified. Study populations were of different races/ethnicities. The mean/median age in all studies

was similar. The majority of patients had serous carcinoma; there were 2 studies focusing exclusively on patients with serous carcinoma [20, 21]. In addition, there were 4 studies focusing exclusively on patients with clear cell carcinoma [22–25]. Most studies used platinum-based chemotherapy, and there was no mention regarding chemotherapy regimens in the remaining 6 studies [10, 12, 20, 22, 26, 27]. The reported median/mean follow-up duration ranged from 22 to 72 months [12, 21, 23, 25, 26, 28–31]. All specimens were tumor tissues. Most studies used immunohistochemistry (IHC) analysis to determine biomarker expression status. Other methods used included immunocytochemistry and real-time quantitative polymerase chain reaction. There was only 1 prospective study [11], and the rest were all retrospective studies [10, 12, 20–36].

Publication Bias

The possibility of publication bias was investigated using a funnel plot. For all biomarkers, we did not find funnel plot asymmetry (Fig. 3). These results were verified by Egger's test (Tables 1, 2).

META-ANALYSIS

The Relationship Between Biomarker Status and OS

PTEN

There were 10 studies that reported an association between PTEN expression and overall survival with univariate analysis, whereas with multivariate analysis, an association between its expression and OS was reported in 4 studies. Neither the meta-analysis of univariate nor of multivariate estimates provided evidence that its status had prognostic value for OS, and considerable heterogeneity existed (Fig. 4; Table 1). When restricted to studies using IHC staining with the 6H2.1 antibody ($n = 2$), patients with reduced PTEN expression were related to poor OS (pooled unadjusted HR = 1.50, 95% CI, 1.03–2.19). There was no heterogeneity between studies.

PI3K

Three studies evaluated an association between PI3K expression and OS with univariate analysis and two studies evaluated this association through multivariate analysis. Only the meta-analysis of multivariate estimates provided evidence that high PI3K expression was significantly related to poor OS in EOC patients (HR obtained from Mantel–Haenszel fixed-effects model: 1.44, 95% CI, 1.08–1.91), although there was moderate heterogeneity ($I^2 = 53.1\%$, $p = .144$).

pAkt

There were 10 studies that reported an association between pAkt expression and OS with univariate analysis and 4 studies with multivariate analysis. Both the meta-analyses of univariate and multivariate estimates showed that high pAkt expression was significantly associated with poor OS (pooled unadjusted HR = 1.16, 95% CI, 1.05–1.29; pooled adjusted HR = 1.60, 95% CI, 1.26–2.04), and there was no heterogeneity between studies.

The Relationship Between Biomarker Status and PFS

A meta-analysis of univariate estimates showed that only high pAkt expression was associated with PFS. In fact, patients with high pAkt were related to poor PFS (pooled HR = 1.24, 95% CI, 1.10–1.39; Fig. 5A; Table 2). There was no heterogeneity between studies.

Five studies were assayed for PFS by multivariate analysis. The results of the meta-analysis showed that patients with high PI3K and pAkt expression were related to poor PFS (HR = 3.35, 95% CI, 1.14–9.82 for PI3K; pooled HR = 1.65, 95% CI, 1.07–2.55 for pAkt; Fig. 5B). There was no heterogeneity between studies. However, there was only one study that reported an association between PI3K expression and PFS with multivariate analysis [34].

DISCUSSION

The PTEN/PI3K/Akt signaling pathway is frequently disrupted in many human cancers, and it is a key player in mediating tumor cell survival and escape from apoptosis [37–39]. The goal of this meta-analysis was to provide a comprehensive, reliable, and current summary of the prognostic and predictive value of the PTEN/PI3K/Akt pathway in EOC patients and to provide a reference for clinical practice. For each biomarker, we gathered data according to OS and PFS, including univariate and multivariate survival analyses.

Earlier studies have shown that PTEN is a tumor suppressor gene. Although deletion or mutation of PTEN has been reported in several types of human tumors, few studies have reported on the relation of PTEN protein level and survival in ovarian carcinomas [40, 41]. In the present study, neither the meta-analysis of univariate nor of multivariate estimates proved to be of significant prognostic value for OS or PFS in EOC patients, and considerable heterogeneity existed. In this meta-analysis, most studies used IHC staining to assess PTEN expression. Although IHC analysis is simple and cost-effective to perform, tremendous variation exists in the experimental procedures, which may influence the results and in part the observed heterogeneity. For example, when restricted to studies using IHC staining with the 6H2.1 antibody, patients with reduced PTEN expression were related to poor OS and PFS and the heterogeneity between studies was reduced.

Although deletion or mutation of PTEN has been reported in several different types of human tumors, few studies have reported on the relation of PTEN protein level and survival in ovarian carcinomas. In the present study, neither the meta-analysis of univariate nor of multivariate estimates proved to be of significant prognostic value for OS or PFS in EOC patients, and considerable heterogeneity existed.

The PI3K/Akt signaling pathway controls many cellular processes, such as the cell proliferation, apoptosis, and motility [42, 43]. A previous study [44] showed that activation scores for PI3K were associated with survival in advanced serous ovarian tumors, which is consistent with our data estimated by the multivariate survival analysis. But for

Figure 4. A forest plot showing results of studies on the prognostic value of the PTEN/PI3K/Akt pathway expression. (A): Unadjusted hazard ratio estimates for OS in patients with these biomarker-positive tumors. (B): Adjusted hazard ratio estimates for OS in patients with these biomarker-positive tumors.

Abbreviations: HR, hazard ratio; OS, overall survival; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog deleted on chromosome 10.

Figure 5. A forest plot showing results of studies on the prognostic value of the PTEN/PI3K/Akt pathway expression. (A): Unadjusted hazard ratio estimates for PFS in patients with these biomarker-positive tumors. (B): Adjusted hazard ratio estimates for PFS in patients with these biomarker-positive tumors.

Abbreviations: HR, hazard ratio; PFS, progression-free survival; PTEN, phosphatase and tensin homolog deleted on chromosome 10.

univariate analysis, no significant correlation between PI3K protein expression and survival was found in EOC patients, and considerable heterogeneity existed. This analysis was affected by the small number of eligible studies, partly as a result of the imperfections in our search strategy. We restricted our meta-analysis to articles published in English and did not search the unpublished data, which would have likely increased the proportions of null views. In addition, there were several studies excluded based on the language restriction. The limitations in our search strategy may have resulted in publication or language bias and may have led to an overestimation of the effect sizes [14].

A previous study showed that activation scores for PI3K were associated with survival in advanced serous ovarian tumors, which is consistent with our data estimated by the multivariate survival analysis. But for univariate analysis, no significant correlation between PI3K protein expression and survival was found in EOC patients, and considerable heterogeneity existed.

Akt is a cytoplasmic serine-threonine protein kinase, whose activation stimulates cell cycle progression, survival,

Table 1. Meta-analysis estimates for overall survival

Factor	Univariate analysis					Multivariate analysis				
	No. of studies	Pooled HR (95% CI)	Heterogeneity <i>p</i> value	<i>I</i> ² (%)	Bias <i>p</i> value	No. of studies	Pooled HR (95% CI)	Heterogeneity <i>p</i> value	<i>I</i> ² (%)	Bias <i>p</i> value
PTEN										
All studies	10	0.99 (0.75–1.29)	.026	49.7	.897	4	0.71 (0.42–1.18)	.047	62.3	.287
Studies using IHC staining with the clone 17.A antibody	2	0.65 (0.26–1.60)	.093	64.6	—	—	—	—	—	—
Studies using IHC staining with the 6H2.1 antibody	2	1.50 (1.03–2.19)	.902	0.0	—	1	1.04 (0.68–1.61)	—	—	—
Studies using IHC staining with the 138G6 antibody	2	1.18 (0.75–1.87)	.078	56.0	—	1	0.82 (0.52–1.30)	—	—	—
PI3K	3	1.17 (0.59–2.30)	.008	74.7	.952	2	1.44 (1.08–1.91)	.144	53.1	—
pAkt										
All studies	10	1.16 (1.05–1.29)	.193	26.4	.483	4	1.60 (1.26–2.04)	.887	0.0	.264
Studies using IHC staining with the 736E11 antibody	2	1.15 (1.00–1.33)	.757	0.0	—	2	1.57 (1.22–2.03)	.510	0.0	—

Abbreviations: —, not applicable; IHC, immunohistochemistry.

Table 2. Meta-analysis estimates for progression-free survival

Factor	Univariate analysis					Multivariate analysis				
	No. of studies	Pooled HR (95% CI)	Heterogeneity <i>p</i> value	<i>I</i> ² (%)	Bias <i>p</i> value	No. of studies	Pooled HR (95% CI)	Heterogeneity <i>p</i> value	<i>I</i> ² (%)	Bias <i>p</i> value
PTEN										
All studies	5	1.26 (0.90–1.78)	.000	77.7	.316	2	0.68 (0.09–4.94)	.001	91.0	—
Studies using IHC staining with the clone 17.A antibody	2	1.04 (0.85–1.26)	.585	0.0	—	—	—	—	—	—
Studies using IHC staining with the 6H2.1 antibody	2	1.76 (1.37–2.27)	.166	38.3	—	1	1.75 (1.11–2.78)	—	—	—
Studies using IHC staining with the 138G6 antibody	1	0.62 (0.44–0.87)	—	—	—	1	0.23 (0.08–0.69)	—	—	—
PI3K	1	1.17 (0.87–1.58)	—	—	—	1	3.35 (1.14–9.82)	—	—	—
pAkt										
All studies	5	1.24 (1.10–1.39)	.281	20.9	.291	2	1.65 (1.07–2.55)	.419	0.0	—
Studies using IHC staining with the 736E11 antibody	2	1.24 (1.03–1.51)	.271	17.5	—	1	1.81 (1.11–2.93)	—	—	—

Abbreviations: —, not applicable; IHC, immunohistochemistry.

metabolism, and migration through phosphorylation of many physiological substrates [9, 45]. Previous studies of Akt in EOC have focused mainly on screening expression levels at the protein or mRNA level. Furthermore, the relation between pAkt status and clinical outcome of EOC patients has not been fully investigated. Although our results show that high pAkt expression was significantly associated with poor OS and PFS, the clinical application for this finding is not recommended because the statistical power of this analysis is limited by a small sample size and the type of studies (mainly retrospective).

In this meta-analysis, almost all studies used a single method to assess the status of biomarkers, which could have made

the data imprecise. In addition, EOC is a heterogeneous tumor that can be classified according to the histology in high-grade serous, endometrioid, clear cell, mucinous, and low-grade serous tumors, and these variants are different in epidemiology, genetic risk factors, molecular events, premalignant lesions, patterns of spread, response to chemotherapy, and prognosis [46]. Unfortunately, there were very few studies included in the present study focusing exclusively on serous ($n = 2$) or clear cell carcinoma ($n = 4$) in which distinct biomarkers were evaluated, so that an analysis regarding a specific histological subtype was not feasible.

Because the current quality assessment scale was mainly designed for the randomized controlled studies and there is

no suitable tool for examining prognostic and predictive biomarker studies, we did not assess the quality of the primary studies [47].

CONCLUSION

Although high pAkt expression is significantly related to poor OS and PFS in EOC patients, this marker alone is unlikely to be used as a predictor for prognosis in clinical practice. Studies using multiple methods to evaluate the expression and activity of Akt and more detailed subanalyses, especially according to histopathological types, would be helpful in validating the value of pAkt as a prognostic predictor in patients with EOC.

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DISCLOSURES

The authors indicated no financial relationships.

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For Further Reading:

Daniela Fischerova, Michal Zikan, Pavel Dundr et al. Diagnosis, Treatment, and Follow-Up of Borderline Ovarian Tumors. *The Oncologist* 2012;17:1515–1533.

Abstract

Borderline ovarian tumors represent a heterogeneous group of noninvasive tumors of uncertain malignant potential with characteristic histology. They occur in younger women, are present at an early stage, and have a favorable prognosis, but symptomatic recurrence and death may be found as long as 20 years after therapy in some patients. The molecular changes in borderline ovarian tumors indicate linkage of this disease to type I ovarian tumors (low-grade ovarian carcinomas). The pathological stage of disease and subclassification of extraovarian disease into invasive and noninvasive implants, together with the presence of postoperative macroscopic residual disease, appear to be the major predictor of recurrence and survival. However, it should be emphasized that the most important negative prognostic factor for recurrence is just the use of conservative surgery, but without any impact on patient survival because most recurrent diseases are of the borderline type—easily curable and with an excellent prognosis. Borderline tumors are difficult masses to correctly preoperatively diagnose using imaging methods because their macroscopic features may overlap with invasive and benign ovarian tumors. Over the past several decades, surgical therapy has shifted from a radical approach to more conservative treatment; however, oncologic safety must always be balanced. Follow-up is essential using routine ultrasound imaging, with special attention paid to the remaining ovary in conservatively treated patients. Current literature on this topic leads to a number of controversies that will be discussed thoroughly in this article, with the aim to provide recommendations for the clinical management of these patients.