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Review Article

The Prognostic Significance of Phosphatase and Tensin Homolog Loss in Breast Cancer

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Abstract

AIM: This study aims to determine the prognostic significance of phosphatase and tensin homolog (PTEN) loss in breast cancer.

METHODS: We conducted a meta-analysis study. Sample of this study were research articles that evaluated PTEN loss and prognosis in breast cancer patients. We searched for relevant studies published in PubMed and Proquest from January 2010 to July 2018. We reviewed studies that examined the association between immunohistochemical expression of PTEN and breast cancer prognosis using meta-analysis methods. Pooled risk ratios (RR) were calculated using fixed and random-effect models. Data were processed using Review Manager 5.3 (RevMan 5.3).

RESULTS: There were 7 studies conducted a systematic review then continued to evaluate the association of PTEN loss and breast cancer prognosis by meta-analysis. There was a significant association of PTEN loss with poor prognosis of breast cancer (RR = 0,76 [95% CI 0,59-0,98 p <0.07), and there was not any significant publication bias for studies included.

CONCLUSION: This study confirmed PTEN loss is an important independent factor for breast cancer prognosis.

Introduction

Breast cancer is the most common malignancies in women worldwide. Breast cancer incidents rapidly increased from 641,000 cases in 1980 to 1.6 million cases in 2010 [1]. GLOBOCAN's 2012 International Agency for Research on Cancer (IARC) data notes that there are approximately 1.67 million new cases of BC diagnosed in 2012 or 25% of all cancers [2].

In Asia Pacific region breast cancer was the most common type of cancer among females, accounting for 18% of all cases in 2012, and was the fourth most common cause of cancer-related deaths (9%). Globally, one of three women (33%) diagnosed with breast cancer in a woman under 50 years old during 2008. The proportion of female breast cancer diagnosed among women under 50 years of age ranged from 21% to 58% in the Asia Pacific region [3].

Prognosis of breast cancer influenced by many factors. Prognostic factors such as tumour size, lymph node involvement and metastasis play a big role in prognosis. Standard adjuvant treatment reduces the risk of disease recurrence and improves prognosis [4]. Most relapses of breast cancer

occurred in the second year of treatment. About 62.71% of patients with primary tumour ≥ 5 cm, 79.65% of patients with ≥ 4 involved of axillary lymph nodes, and 72.41% of hormone receptor-negative tumours could relapse. Large tumour size, number axillary lymph nodes metastasis, and hormone receptor status were strongly associated with risk of relapse [5].

One biomarker of breast cancer growth is phosphatase and tensin homolog (PTEN). PTEN dysfunction on tumour cells causes increasing of NF-kB activity resulting in growth, proliferation, survival, and metabolism of tumour cells [6], [7], [8]. Previous studies revealed tumour cells with PTEN loss of function have a poor prognosis [9], [10], [11], [12]. But there are also studies showed different results [13]. Changes of PTEN expression can be accurately identified by Immunohistochemical analysis (IHC). IHC analysis is quicker and more cost-effective than molecular genetic techniques to detect PTEN status. Therefore, this study aims to determine the prognostic significance of PTEN loss in breast cancer by IHC methods using meta-analysis.

Material and Methods

Study design and research sample

This study was quantitative with meta-analysis study design. The meta-analysis followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) Statement. Meta-analysis was used to determine the association between PTEN loss expression and breast cancer prognosis. The result of published articles on the internet through databased on PubMed and Proquest that published from January 2010 to August 2018 were analysed. The inclusion criteria of this study were cohort studies. Exclusion criteria of this study were articles which are not available in full-text form.

Operational definitions

The variables of this study are PTEN loss expression as an independent variable, and a dependent variable is a prognosis.

Research procedure

This study was conducted by collecting data through the identification of published research articles on the association between PTEN loss expression and breast cancer prognosis by using the PubMed and Proquest search engines (Figure 1).

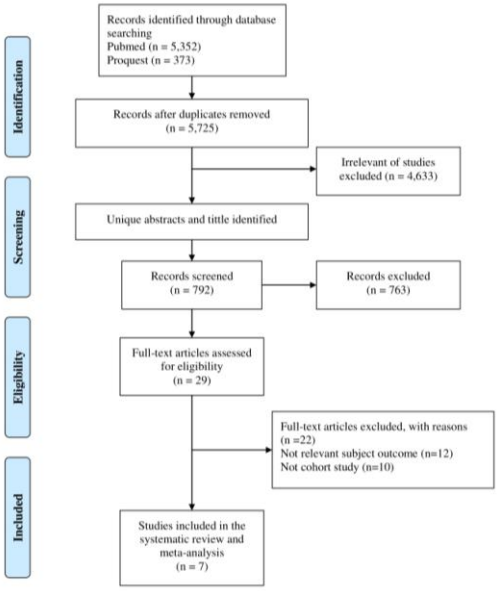

Figure 1: Flow diagram research procedure

Identification of 5,725 articles, reviewed through the title of the articles, continued by reviewing the abstract, and then the full-text form. The article was excluded if: (a) not the relevant subject outcome, (b) the information provided in the results was insufficient for data extraction and (c) duplicate studies.

Data collection technique

The search was limited to English language articles. The article type was limited to research articles. The research subject was limited to a human subject. The time of publication was limited from January 2010 to August 2018 period. The abstract of articles with relevant title continued to review process, and the articles with the irrelevant title were excluded. After that, articles with relevant abstract were continued to be reviewed in full-text, while the others were excluded. The articles that used immunohistochemistry method only and the relevant outcome will be reviewed and analysed.

Data analysis

The analysis was conducted to obtain the value of pooled risk ratio as the combined risk ratio value from the collected researches. Data analysis was performed using the Mantel-Haenszel method with a fixed-effect model and the DerSimonian-Laird random-effect model. Publication bias was visually evaluated by using funnel plots and statistically assessed through Egger's and Begg's tests. Meta-analysis was carried out by using *Review Manager* 5.3 (RevMan 5.3).

Results

The selection of studies was conducted to identify 7 studies related to the PTEN loss expression. The characteristic of eligible studies (Table 1). These publications estimate association between PTEN loss expression and prognosis with various sample size, staining methods, cut off and methods of interpretation.

Table 1. A systematic review of the role of loss of PTEN expression in breast cancer prognosis

First Author	Procedure	Histology typing	Cut off	Staining methods	Number of patients	Scoring	Outcome
Jensen et al., [11]	IHC	mixed	> 40	Cytoplasmic	235	IRS	OS
Wu et al., [14]	IHC	TN	> 5	Cytoplasmic	65	IRS	OS
Perez et al., [15]	IHC	mixed	> 0	Nuclear / cytoplasmic	1286	SI	DFS/OS
Tang et al., [16]	IHC	mixed	> 0	inti	68	SI	OS
Beelen et al., [17]	IHC	mixed	> 3	Cytoplasmic	436	SI	OS
Stern et al., [18]	IHC	mixed	> 5	Cytoplasmic	2354	SI	DFS/OS
Beg et al., [19]	IHC	Mixed	> 90	Nuclear and cytoplasmic	957	H-score	OS

Abbreviation: IHC: Immunohistochemistry; TN: Triple-negative; IRS; immunoreactive score; SI: Staining intensity; OS: overall survival; DFS: disease-free survival.

Forest plots of PTEN loss expression in breast cancer prognosis (Figure 2). Figure 2 revealed the significance association of PTEN loss expression with prognosis of breast cancer (RR = 0.76 [95% CI = 0.59-0.98, p < 0.07]).

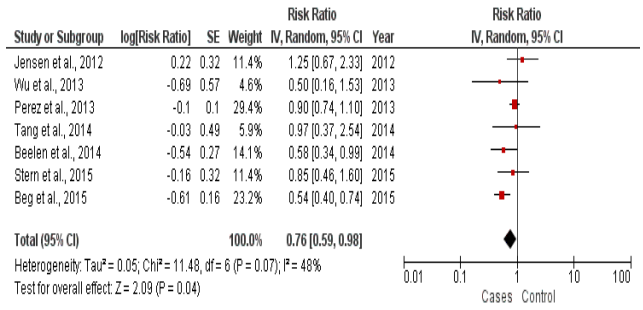

Figure 2: Forest plots the association of PTEN loss and breast cancer prognosis

Funnel plot association of PTEN loss expression with breast cancer prognosis (Figure 3).

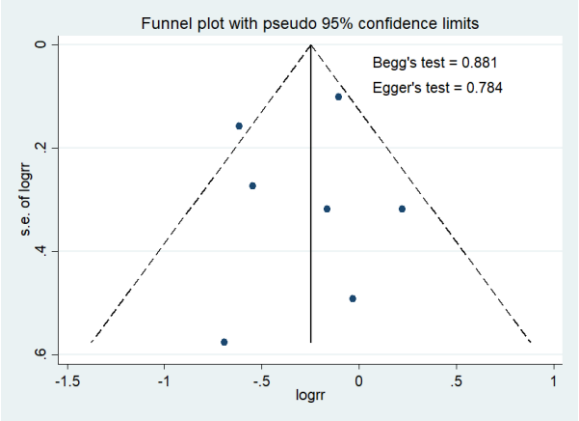

Figure 3: Funnel plots the association of PTEN loss and breast cancer prognosis

Figure 3 showed the association of PTEN loss expression with the prognosis of breast cancer has a variety of homogeneous research on breast cancer. It means that if the analysis is done on the population, time and place and different conditions the results will be consistent. There was not any significant publication bias for the association of PTEN loss expression with breast cancer prognosis, Egger's test (P = 0.784) and Begg's test (P = 0.881).

Discussion

Identification of biomarkers and gene expressions are needed to improve early diagnosis and prognosis, as well as to provide the most effective drug suitable with molecular characteristics of the patients. Studies over the years have indicated that prognostic and predictive biomarkers are molecules involved in the regulation of cellular mechanisms, including proliferation, apoptosis, angiogenesis, metastasis and therapeutic resistance. Evidence has shown that PTEN is an important factor in many processes related to cancer progression [20], [21].

PTEN is one of the tumour suppressor genes that play a role in breast cancer development. PTEN is an antagonist of phosphatidylinositol 3-kinase (PI3K) and plays a role in dephosphorylation of PIP3 into PIP2. Loss of PTEN can cause overgrowth, proliferation, survival, and metabolism of tumour cells. PTEN consists of phosphatase homolog and cytoskeletal tensin protein. PTEN protein contains 403 amino acids. The crystal structure of PTEN consists of two main functional domains (phosphatase domain and C2 domain) and three structural PIP2 binding domains, C-terminal tail [22]. PTEN loss can also cause phosphorylation mediated by Akt and increase of NF-kB activity which promotes P53 degradation. P53 degradation reduced the apoptotic ability and induced cell cycle progression [8]. PTEN gene located on chromosome 10q23. Loss of heterozygosity on chromosome 10q23 often occurs in advanced sporadic tumours, including breast cancer [23]. PTEN dysfunction, especially its inactivity in tumour cells, causes PIP3 accumulation in cells and regulate Akt recruitment. Furthermore, it can activate downstream kinases, increasing NF-kB activity resulting in growth, proliferation, survival, and metabolism of tumour cells [6], [7], [24].

Some studies suggested PTEN loss in tumour cells are associated with drug resistance [6,15]. Other studies showed a significant association between PTEN immunoscoring and mRNA expression. A previous study also revealed that PTEN loss has a significantly worse prognosis than PTEN positive breast cancer cells [17], [18]. PTEN loss is also associated with aggressive behaviour and poor prognosis [14], [19].

Changes of PTEN expression can be identified by IHC analysis, Fluorescent In situ Hybridization (FISH) and PCR. There were previous meta-analyses of PTEN loss, but it did not elaborate on the methods. The previous study found IHC analysis is quicker and more cost-effective than molecular genetic techniques to detect PTEN expression [25], [26]. FISH and PCR is limited to sophisticated laboratories; it cannot be done routinely. In a developing country, not all laboratories have FISH and PCR services. This study answers the need for an analysis of the association of PTEN with prognosis in the use of IHC staining methods.

This study has identified the heterogeneity of published articles ($p = 0,04$, $I^2 = 45\%$), then used the random effect models. The analysis revealed significance association of PTEN loss with prognosis of breast cancer (RR = 0.76 [95% CI = 0.59-0.98, $p < 0.07$]). The pooled finding of these seven articles provides evidence of the significance of PTEN loss of expression with prognosis. This meta-analysis showed that PTEN could provide prognostic information for the clinician during the decision-making process.

Although we try to make our study as good as possible, the limitation of this study should be considered. First, data suitability of several studies included in this meta-analysis showed different sample sizes (65-2354 samples). Second, there are different scoring methods for PTEN status with different numbers of positivity of tumour cells. The study was using immunohistochemical analysis and could be carried out with different evaluation methods using IS (intensity staining), histoscore (H-score) and percentage of positive cells. Different studies with different PTEN classifications and different patient sets are hardly comparable.

Cut off points are varying from > 0% to > 90%. These differences in the method could be responsible for various PTEN expression observed in tumour cells. Although the robustness of PTEN antibodies has been controversy, optimal IHC conditions including concentration of anti-PTEN antibody as well as different antigen retrieval conditions should be considered too. Scoring methods against PTEN's requires a more valid and reliable standard methodology to assess PTEN expression. In conclusion, the result of this meta-analysis showed that loss PTEN expression is associated with poor prognosis of breast cancer.

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