Clinica Chimica Acta 483 (2018) 209–215

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Review

Prognostic and clinical significance of histone deacetylase 1 expression in breast cancer: A meta-analysis

Weiqiang Qiao[a], Heyang Liu[b], Ruidong Liu[c], Qipeng Liu[a], Ting Zhang[a], Wanying Guo[a], Peng Li[a], Miao Deng[a,*]

[a] Department of Breast Surgery, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China
[b] Department of Oncology, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang 471003, China
[c] Department of Breast Surgery, The First Affiliated Hospital of Henan University of Traditional Chinese Medicine, Zhengzhou 450000, China

ARTICLE INFO

Keywords:
Breast cancer
HDAC1
Prognosis
Meta-analysis

ABSTRACT

Background: There are conflicting reports about the role of histone deacetylase 1 (HDAC1) in breast cancer prognosis. Here, we conducted a meta-analysis to investigate the prognostic significance of HDAC1 in breast cancer.

Materials and methods: We searched different databases to identify studies evaluating the association between HDAC1 expression and its prognostic value in breast cancer. The pooled hazard ratios (HRs) and odds radios (ORs) with 95% confidence intervals (95% CIs) were calculated from these studies to assess specific correlation.

Results: Our meta-analysis of four databases identified 7 eligible studies with 1429 total patients. We found that HDAC1 over-expression did not correlate with disease-free survival (DFS) and overall survival (OS) in breast cancer. Subgroup analysis indicated an association between up-regulated HDAC1 expression and better OS (HR = 0.47, 95% CI: 0.23–0.97; P = 0.04) in Asian breast cancer patients. However, false-positive report probability (FPRP) analysis and trial sequential analysis (TSA) indicated that the results need further validation. Furthermore, HDAC1 over-expression was associated with positive estrogen receptor (ER) expression (OR, 3.30; 95% CI, 1.11–9.83; P = 0.03) and negative human epidermal growth factor receptor 2 (HER2) expression (OR, 1.79; 95% CI, 1.22–2.61; P = 0.003), but there were no significant differences between patients based on age, tumor size, lymph node metastasis, nuclear grade, or progesterone receptor (PR) expression.

Conclusion: Overall, our meta-analysis demonstrated an association between increased HDAC1 expression and better OS in Asian breast cancer patients. In addition, HDAC1 over-expression correlated with positive ER and negative HER2 expression in breast cancer. However, researches in large patients' randomised controlled trials (RCTs) are needed to confirm the results.

1. Introduction

Breast cancer is a highly common cancer in females and poses a serious health challenge. It is estimated that approximately 266,120 cases of female breast carcinoma will be diagnosed during 2018 in the United States alone [1]. Similarly, the incidence rate of breast cancer in China is close to 15% [2]. Interestingly, due to identification of various subtypes of breast cancer markers, including the estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki67, breast cancer prognosis has improved due to the development of subtype specific treatments [3]. However, significant heterogeneity among different breast cancer subtypes has greatly influenced overall therapeutic efficacy, especially in the triple-negative breast cancer (TNBC) subtype. Therefore, it is necessary to identify novel molecular biomarkers that can effectively guide clinical diagnosis, treatment, and prognosis in breast cancer patients.

Histone deacetylases (HDACs) are a family of proteins consisting of 18 members stratified into four sub-classes (Group I, IIa and IIb, III and IV). All HDAC members play an important role in gene transcription, but HDAC1 has been described as a crucial epigenetic factor. Moreover, many HDAC inhibitors have been suggested as potential therapeutic targets, not only in cancer but also in other clinical diseases [4,5]. Multiple studies have demonstrated the important role of HDAC1 in regulating proliferation, differentiation, invasion, and apoptosis of tumor cells, through transcriptional inhibition of tumor suppressor genes, and thereby influencing cell cycle events [6,7]. Tang et al. reported that HDAC1 induced proliferation and migration of breast cancer cells through activating Snail/interleukin-8 (IL-8) signals [8].

* Corresponding author.
E-mail address: dengmiao1973@163.com (M. Deng).

https://doi.org/10.1016/j.cca.2018.05.005
Received 13 March 2018; Received in revised form 3 May 2018; Accepted 4 May 2018
Available online 05 May 2018

Other independent studies have also confirmed a correlation between HDAC1 expression and clinicopathological features of multiple cancers, including breast cancer [9], gastric cancer [10], hepatocellular carcinoma [11], gallbladder cancer [12], pancreatic cancer [13], colorectal cancer [14], lung cancer [15], and mobile tongue squamous cell carcinoma [16].

Importantly, several studies have supported the correlation between increased HDAC1 expression and favorable prognosis of breast cancer [17,18], but one study demonstrated conflicting data [19], disputing the general conclusion that HDAC1 expression is correlated with breast cancer prognosis. Therefore, the present meta-analysis was conducted to further evaluate the association between HDAC1 expression and breast cancer patient survival. In addition, we performed a comprehensive analysis of the correlation between HDAC1 expression and breast cancer clinicopathological factors.

2. Materials and methods

2.1. Search strategy

All published studies through January 20, 2018 were identified using PubMed, Embase, the Cochrane Library, and Web of Science databases. The search strategy consisted of the following medical subject headings (MeSH) in combination; “breast neoplasms”/“breast cancer”, and “histone deacetylase 1”/“HDAC1”.

2.2. Inclusion and exclusion criteria

The following inclusion criteria were used to select relevant studies: (1) all studies included breast cancer patients; (2) all studies reported on the association between HDAC1 expression and clinical factors and breast cancer prognosis; and (3) all studies clearly defined “high” and “low” or “positive” and “negative” levels of HDAC1 expression. Studies were excluded if they: (1) exclusively used cell lines or animals, (2) were reviews, abstracts, letters, or case reports, or (3) had insufficient data to assess the association between HDAC1 expression and clinical features or breast cancer survival outcomes.

2.3. Data extraction

Data extraction was undertaken by two authors independently; the primary extracted information included: first author surname, year, type of population, number of patients, age, follow-up duration, survival outcome, detection method, cut-off values, and proportion of high HDAC1 level. Hazard ratios (HRs) were extracted from the text, tables, or Kaplan-Meier curves provided in these studies. Prognostic information was digitized using Engauge Digitizer Version 4.1 (http://markummitchell.github.io/engauge-digitizer/) software, from the Kaplan-Meier curves. The Newcastle Ottawa Scale (NOS) was used to assess the quality of eligible studies [20]. The NOS consisted of eight categories scored 0 to 9; a score of 7 or higher represented high study quality.

2.4. Statistical analysis

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were used in our meta-analysis [21]. To assess the association between HDAC1 expression and prognosis, pooled HRs with 95% confidence intervals (CIs) were extracted from the Kaplan-Meier curves using the method described by Tierney et al. [22]. The odds ratios (ORs) with 95% CIs were also applied to evaluate the correlation between HDAC1 expression and clinical parameters. Heterogeneity between studies was estimated using the Q test and I^2 statistics [23]. A P value < 0.05 and I^2 value $> 50\%$ indicated notable heterogeneity; hence, the random effects model was used in our meta-analysis [24]. In other cases, we used the fixed effects model for analysis. To explore the source of heterogeneity, we also performed meta-regression analysis. Publication bias was detected using the Begg's and Egger's tests [25,26]. Sensitivity analysis was undertaken by excluding one study at a time. False-positive report probability (FPRP) analysis and trial sequential analysis (TSA) were performed to assess the significant associations [27,28]. All statistical analyses were conducted using Review Manager version 5.3 (Cochrane Collaboration, Copenhagen, Denmark) and STATA version 12.0 (Stata Corporation, TX, USA) software, and all statistical tests were two-sided, with a P value of < 0.05 representing statistical significance.

3. Results

3.1. Identification of relevant studies

Our initial search based on the selection criteria identified 529 potential studies. Among these, 183 were duplicate studies and were therefore excluded. After reviewing the titles and abstracts of the remaining studies, 307 studies were excluded because they either involved non-human subjects or were abstracts, case reports, or book chapters. After fully reviewing 39 studies, 32 were further excluded due to the following reasons; reviews (n = 7), no study endpoint (n = 11), or insufficient data (n = 14). Finally, 7 studies involving 1429 patients were included in our overall analysis [17–19,29–32]. The complete study selection process is summarized in Fig. 1.

3.2. Characteristics of eligible studies

Detailed characteristics of the eligible studies are shown in Tables 1 and 2. Among the 7 included studies, 5 studies were from Asia and 2 were from Europe. HDAC1 expression in 6 studies was analyzed using immunohistochemistry (IHC), while one other study used real-time polymerase chain reaction (RT-PCR). However, the cut-off values defining HDAC1 expression as high or low varied across all studies. The proportion of high HDAC1 levels ranged from 32.7% to 81.3%. Overall, all eligible studies reported information about the correlation between HDAC1 expression and breast cancer clinical parameters. It is important to note that all included studies were observational in nature, but all appeared to be high quality studies based on the NOS criteria of quality assessment (score ≥ 7).

3.3. Correlation between HDAC1 expression and patient survival

Among the 7 included studies, only 3 reported information about the relationship between HDAC1 expression and disease-free survival (DFS) in breast cancer patients. Since significant heterogeneity (P = 0.01, I^2 = 77%) was observed between these studies, our meta-analysis was performed using random-effects model. Our data indicated no association between high HDAC1 expression and DFS (HR, 0.55; 95% CI, 0.24–1.28; P = 0.16; Fig. 2). To further explore the reasons for significant heterogeneity, a subgroup analysis was performed based on HDAC1 expression (protein or mRNA). Interestingly, no heterogeneity was observed in the subgroup analysis with regards to HDAC1 protein expression (P = 0.63, I^2 = 0%). However, in this subgroup analysis, we observed no correlation between HDAC1 protein expression and breast cancer patient DFS (HR = 0.86, 95% CI: 0.55–1.34; P = 0.50; Fig. 2).

In addition, the correlation between HDAC1 expression and breast cancer patient overall survival (OS) was assessed based on data from 6 eligible studies. Here again, due to the significant heterogeneity among these studies (P = 0.0004, I^2 = 78%), the meta-analysis was performed using random effects model. No significant association was observed between increased HDAC1 expression and breast cancer patient OS (HR, 0.67; 95% CI, 0.36–1.24; P = 0.21; Fig. 3). However, patient stratification, based on location, revealed significant correlation between HDAC1 over-expression and better OS in Asian breast cancer patients (HR = 0.47, 95% CI: 0.23–0.97; P = 0.04; Fig. 3).