

Original Article

Aldehyde dehydrogenase 1 expression correlates with clinicopathologic features of patients with breast cancer: a meta-analysis

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Received March 11, 2015; Accepted May 25, 2015; Epub June 15, 2015; Published June 30, 2015

Abstract: A number of studies have investigated the relationship between aldehyde dehydrogenase 1 (ALDH1) expression and the clinical pathological features of the patients with breast cancer. However, conclusions reported by different parties seem to be inconsistent. We have reviewed published studies and carried out this meta-analysis to provide credible results. We searched PubMed for articles published in English until September 12, 2014. Our main analyses were focused on the association between ALDH1 and the clinical pathological features, such as age, tumor size, nodal status, lymphovascular invasion, histological grade, and the expression of ER, PR, and HER2 by meta-analysis methods. If heterogeneity was observed, we used random effects model to calculate the overall odds ratios, otherwise fixed effects model was used. Twenty-one eligible studies were included in the present meta-analysis. From the pooled analyses, there was significant association between ALDH1 expression and histological grade (low vs. intermediate: pooled OR = 1.51, 95% CI: 1.09-2.10, $P = 0.01$; intermediate vs. high: pooled OR = 1.86, 95% CI: 1.12-3.07, $P = 0.02$), ER expression (pooled OR = 0.41, 95% CI: 0.29-0.58, $P < 0.00001$), and PR expression (pooled OR = 0.56, 95% CI: 0.40-0.77, $P = 0.0004$). No clear correlation was found between ALDH1 expression and age, tumor size, lymph node (LN) metastasis, lymphovascular invasion, and HER2 expression ($P > 0.05$). Despite the inconsistency in the published reports, this meta-analysis provides credible evidence to support the association between ALDH1 and breast cancer. However, it is necessary to conduct large sample studies using standardized and well-matched controls.

Keywords: Breast cancer, ALDH1, ER, PR, histological grade

Introduction

Breast cancer is a heterogeneous disease, comprising various histological types, with distinct clinical presentations and underlying molecular signatures [1]. Aldehyde dehydrogenase 1 (ALDH1) is an aldehyde dehydrogenase, responsible for oxidation of retinol to retinoic acid, important for normal development and homeostasis in several organs and crucial during embryogenesis [2]. Mammary stem cells, as identified by cells expressing the marker ALDH1, appear to be correlated with malignant transformation of breast tissue [3]. ALDH1 expression has been related to poor clinical outcome, absence of estrogen and progesterone receptors, and expression of basal cytokeratins in prior studies of human breast cancers [4, 5].

To date, numerous studies have investigated the association between ALDH1 expression and breast cancer. To provide a broad description of the relationship of ALDH1 to breast cancer, we do not concentrate on a single primary analysis, but we conducted a meta-analysis of all published studies to assess the robustness of the relationship between ALDH1 expression and clinicopathologic parameters of breast cancer patients.

Materials and methods

Publication search and data extraction

The electronic database PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) was searched by using the following search terms: "ALDH1" and "breast cancer". Letters to the editor,

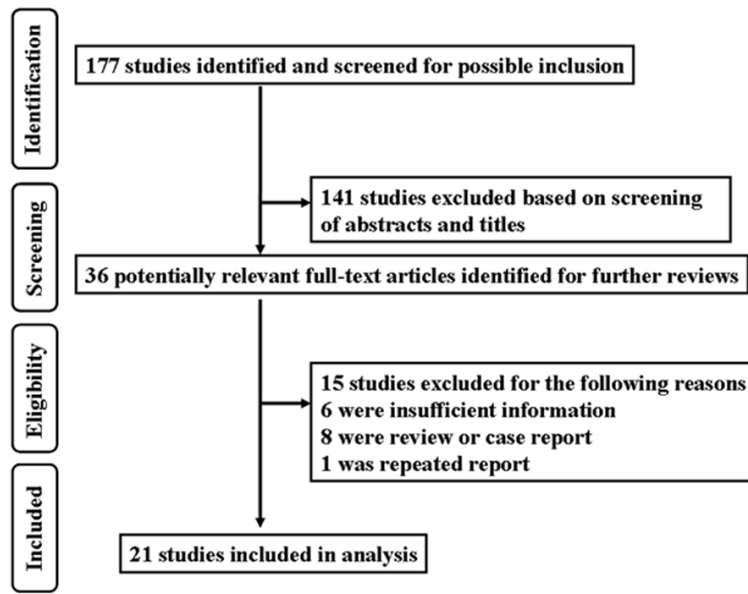


Figure 1. Flow diagram of identifying potential studies in our meta-analysis.

reviews, and articles published in a book or papers published in non-English language were excluded. However, these articles were also scanned to find additional eligible studies. Studies were included when the following criteria were met: (1) published in English with the full text available, (2) the use of a case control design or a cohort design, and (3) the availability of data to allow the estimation of the odd ratios (OR) for survival with a 95% CI. The review process was performed by two independent reviewers (first author and third author).

The following information was recorded for each study: first author's name, year of publication, patient source, number of cases, age, and test method. Information was carefully extracted from all eligible publications independently by two of the authors of the present study (first author and third author). Differences in the extraction of data were checked by a third investigator (corresponding author). After extraction, data were reviewed and compared by the other two independent investigators (second author and fourth author). Disagreements between the two extractors were resolved by consensus among the investigators.

Meta-analysis

For the quantitative aggregation of results, odd ratios (OR) and their 95% confidence intervals (CIs) were combined to give the effective value.

Clinicopathological factors were sorted into several subgroups: age, tumor size, nodal status, lymphovascular invasion, histological grade, and the expression of ER, PR, and HER2. Fixed and random effects models were used to calculate a pooled OR. Q and I^2 statistics were used to examine whether the results of studies were homogeneous [6]. Analysis was performed using Review Manager (RevMan) (Version 5.0 for Windows, The Cochrane Collaboration, 2003). $P < 0.05$ was considered statistically significant.

Results

Search results

One hundred and seventy-seven articles were identified initially using the search strategy above. Close screening of these 177 studies excluded 155 because of the following reasons: non-human studies, insufficient information, review, or letter to editor. Two of the remained 22 papers were previously written by the same author (Zhong et al. [7] and [12]), we selected the latest one [12]. Eventually, 21 eligible studies were included in the present meta-analysis [8-28]. The study selection procedure is showed in **Figure 1** and the study characteristics are displayed in **Table 1**.

ALDH1 expression and breast cancer

No clear correlation was found between ALDH1 expression and age (pooled OR = 0.92, 95% CI: 0.73-1.17, $P = 0.52$) (**Figure 2**), tumor size (pooled OR = 1.10, 95% CI: 0.85-1.43, $P = 0.46$) (**Figure 3**), lymph node (LN) metastasis (pooled OR = 1.08, 95% CI: 0.88-1.32, $P = 0.47$) (**Figure 5**), and lymphovascular invasion (pooled OR = 0.79, 95% CI: 0.43-1.45, $P = 0.45$) (**Figure 6**). ALDH1 expression was associated with histological grade (low vs. intermediate: pooled OR = 1.51, 95% CI: 1.09-2.10, $P = 0.01$; intermediate vs. high: pooled OR = 1.86, 95% CI: 1.12-3.07, $P = 0.02$) (**Figure 4**), ER expression (pooled OR = 0.41, 95% CI: 0.29-0.58, $P < 0.00001$) (**Figure 7**), and PR expression (pooled OR = 0.56, 95% CI: 0.40-0.77, $P = 0.0004$) (**Figure 8**), while not associated with HER2

ALDH1 and breast cancer

Table 1. Characteristics of studies included in the meta-analysis

First author	Year	Country	Ages (mean)	Cases	Method	Antibody
Gong [8]	2014	America	49	74	IHC	BD Biosciences 1:100
Yoshioka [9]	2011	Japan	52	257	IHC	BD Biosciences 1:1000
Ohi [10]	2011	Japan	56	106	IHC	BD Biosciences 1:1000
Tan [11]	2013	Singapore	32	141	IHC	Abcam 1:100
Zhong [12]	2014	China	Not shown	121	IHC	Abcam 1:100
Kim [13]	2014	Korea	58	428	IHC	Abcam 1:100
Nogami [14]	2014	Japan	53	40	IHC	BD Biosciences 1:200
Madjd [15]	2012	Iran	48	127	IHC	Abcam 1:250
De Brot [16]	2012	Brazil	55	140	IHC	Epitomics 1:150
Dong [17]	2013	China	49	161	IHC	BD Biosciences 1:200
Tsukabe [18]	2013	Japan	Not shown	194	IHC	BD Biosciences 1:100
Kang [19]	2014	Korea	45	425	IHC	BD Biosciences 1:100
Charafe-Jauffret [20]	2010	America	Not shown	109	IHC	BD Biosciences 1:100
Sakakibara [21]	2012	Japan	Not shown	115	IHC	BD Biosciences 1:200
Lee [22]	2011	Korea	46	92	IHC	BD Biosciences 1:100
Alamgeer [23]	2014	Australia	Not shown	134	IHC	BD Biosciences 1:200
Nalwoga [24]	2010	Uganda	46.2	192	IHC	BD Biosciences 1:250
Schwartz [25]	2013	Ghana	46	173	IHC	BD Biosciences 1:500
Morimoto [26]	2009	Japan	52.6	203	IHC	BD Biosciences 1:100
Yu [27]	2010	China	56	96	IHC	Abcam 1:100
Mieog [28]	2012	Netherlands	Not shown	574	IHC	BD Biosciences NA

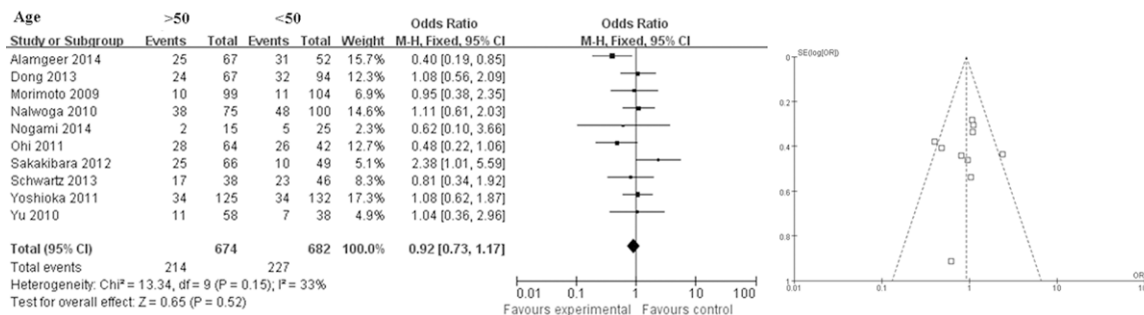


Figure 2. Forest plot and funnel plot for ALDH1 expression and the age of the patients with breast cancer.

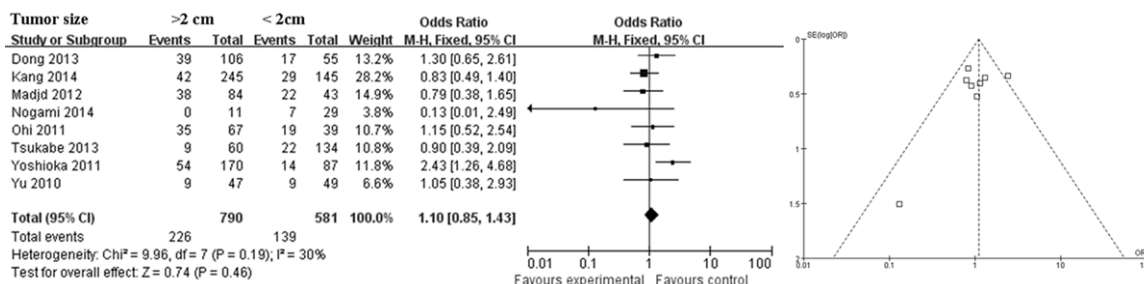


Figure 3. Forest plot and funnel plot for ALDH1 expression and tumor size.

expression (pooled OR = 1.45, 95% CI: 0.98-2.13, P = 0.06) (Figure 9). No obvious publica-

tion bias was observed in these studies (Figures 2-9).

ALDH1 and breast cancer

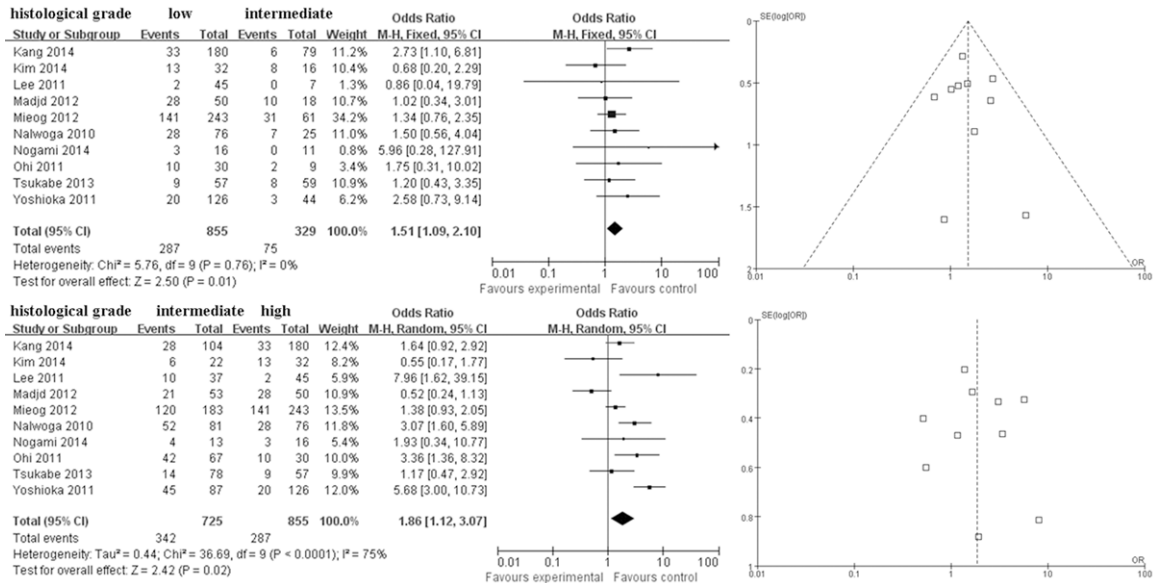


Figure 4. Forest plot and funnel plot for ALDH1 expression and histological grade.

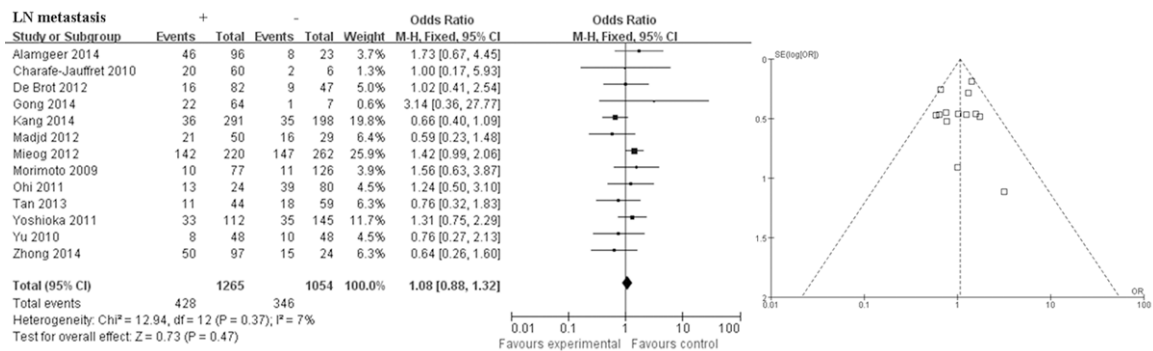


Figure 5. Forest plot and funnel plot for ALDH1 expression and LN metastasis.

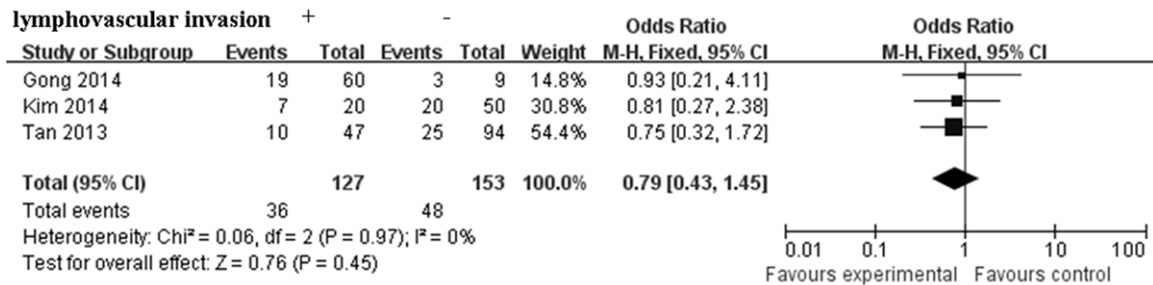


Figure 6. Forest plot and funnel plot for ALDH1 expression and lymphovascular invasion.

Discussion

In the present meta-analysis, we have combined 21 published papers to evaluate the association between ALDH1 expression and the pathologic characteristics of breast pati-

ents known to be important for the clinical outcome, such as tumor size, nodal status, hormonal receptor status. ALDH1 may have a role in early differentiation of stem cells and stem cell proliferation through its role in oxidizing retinol to retinoic acid, a modulator of cell prolif-

ALDH1 and breast cancer

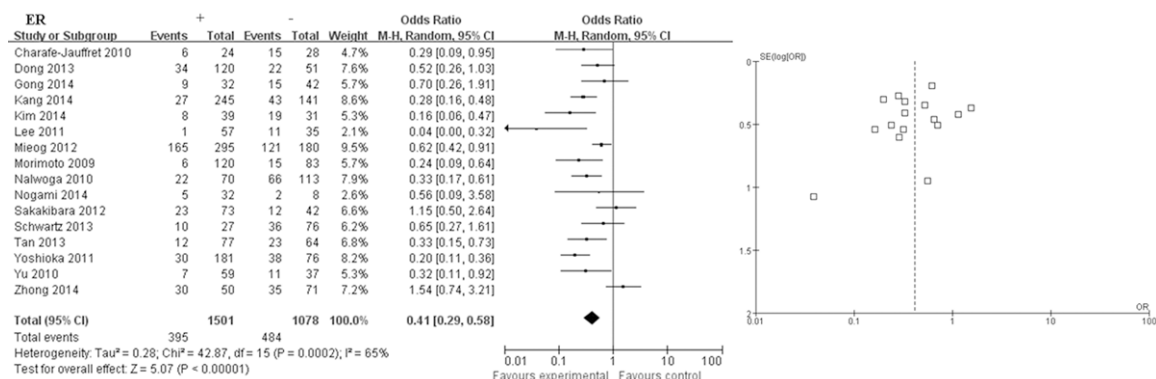


Figure 7. Forest plot and funnel plot for ALDH1 expression and ER expression.

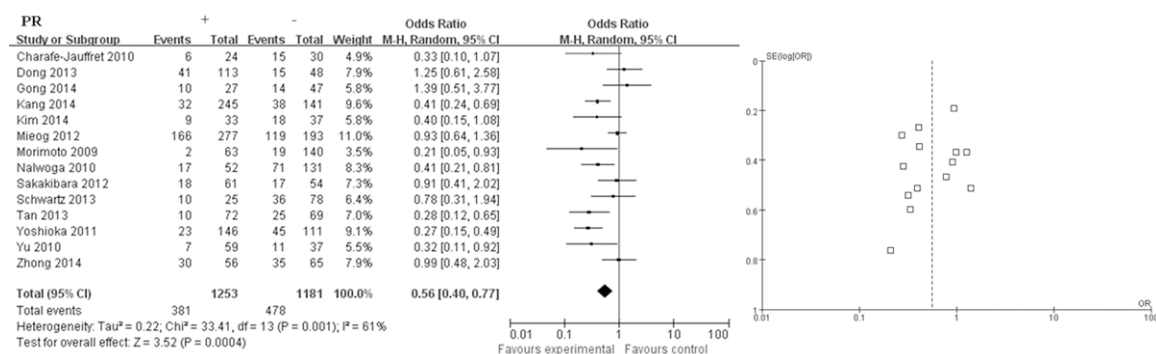


Figure 8. Forest plot and funnel plot for ALDH1 expression and PR expression.

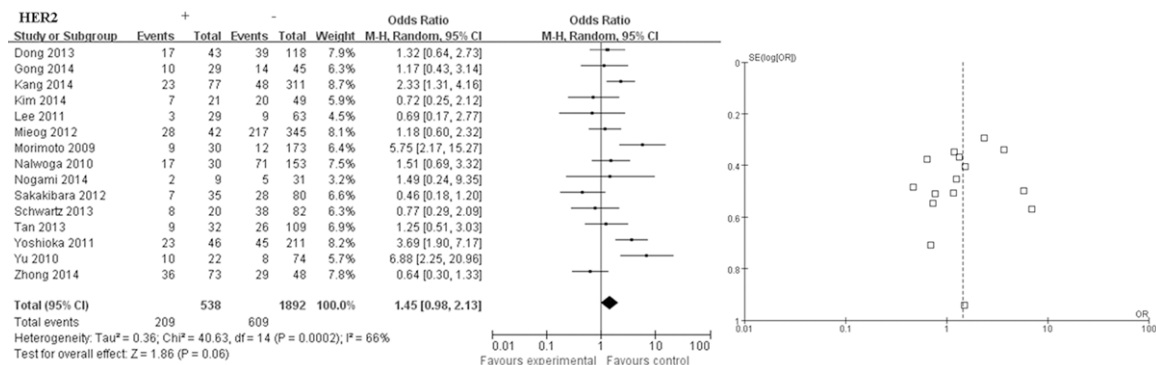


Figure 9. Forest plot and funnel plot for ALDH1 expression and HER2 expression.

eration [29]. ALDH1 expression has been employed for identification of human cancer stem cells [30-32]. Several studies have assessed ALDH1 expression by immunohistochemistry in breast tissue, either in nonmalignant or malignant breast tumors in order to define ALDH1 role and impact in predicting cancer development [7-28]. Since the first report by Ginestier et al. [33] showed ALDH1 expression was associated with poor clinical outcome in

human breast cancer, more and more studies provided evidence that a significant association between ALDH1 expression and the patients' clinical outcome [7-28]. However, these findings are not without controversy. Due to the complexity of disease, it is likely that only combinations of previous studies will provide more credible results. Resetkova et al. [34] showed that tumoral stromal expression of ALDH1 by immunohistochemistry was associ-

ated with survival of triple negative invasive breast carcinomas.

Triple negative breast cancer (TNBC) [negative for expression of estrogen and progesterone receptors (ER, PR) and HER2/neu protein] represent a subtype of breast cancer associated with poor prognosis and highly aggressive behavior [35]. Our pooled results confirmed that ALDH1 expression was associated with histological grade, ER expression, and PR expression. However, we didn't find any association of ALDH1 and HER2. To our knowledge, although ALDH1 could be used as an independent marker for breast cancer, the mechanisms of ALDH1 in breast cancer remains unclear. Intensive studies were needed to elucidate the intrinsic mechanism.

Some limitations of this meta-analysis should be taken into account. Firstly, the results calculated in our meta-analysis may have bias as we only collected full published papers and articles published in English. Secondly, because of inability to obtain raw data, we could perform only a study-level but not a patient-level meta-analysis, which would have enabled us to adjust for multiple risk factors. In the last, case selection, technique, and interpretation also raise the discrepancy of each study. For example, the cutoff value of immunohistochemistry was defined differently in each study.

In conclusion, despite the inconsistency in the published reports, this meta-analysis provides credible evidence to support the association between ALDH1 and breast cancer. However, it is necessary to conduct large sample studies using standardized and well-matched controls.

Acknowledgements

The authors would like to thank Ms. Ying Xu (China Medical University) for editing and reviewing of the manuscript.

Disclosure of conflict of interest

None.

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ALDH1 and breast cancer

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ALDH1 and breast cancer

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