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Review Article

Clinicopathological and prognostic values of ALDH1 in epithelial ovarian cancer: a meta-analysis

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Abstract: Background: Previous studies have confirmed the prognostic value of positive aldehyde dehydrogenase 1 (ALDH1) expression for ovarian cancer, but its predictive value remains controversial. Methods: Meta-analysis was conducted to clarify the correlation of positive ALDH1 expression with the clinicopathological characteristics, types, overall survival and progression-free survival of epithelial ovarian cancer. PubMed, EMBASE and Cochrane were comprehensively searched through July 2017. Nine studies were included. Results: High ALDH1 expression was significantly correlated with the International Federation of Gynecology and Obstetrics (FIGO) stage of ovarian cancer in both Chinese and Caucasians, and with tumor grade in Chinese people (pooled OR and 95% CI = 2.10 (1.20, 3.67)), but not with lymph node metastasis (2.47 (0.77, 7.87)) or tumor location in the ovary (1.10 (0.62, 1.96)). ALDH1 expression was correlated with subtypes of epithelial ovarian cancer (e.g. serous carcinoma, mucinous carcinoma and endometrioid carcinoma) in Caucasians and with the overall survival (1.59 (1.11, 2.29)), but not with progression-free survival (1.14 (0.72, 1.82)). Conclusions: Positive ALDH1 expression is significantly correlated with the clinicopathological characteristics and prognosis of ovarian cancer.

Keywords: ALDH1, epithelial ovarian cancer, meta-analysis

Introduction

Ovarian cancer is the fourth most common gynecologic malignancy in women and the leading death cause of patients with gynecological cancers worldwide [1]. Ovarian cancer has only a few symptoms and is often detected at late stage with poor prognosis [2, 3]. More than 60% of women diagnosed with ovarian tumors are accompanied by an advanced-stage disease, in which tumor cells have already spread beyond the ovaries with implantation or ascites. The diagnosed ovarian cancers originated mostly from the epithelium and slightly from stromal or germ cells [4, 5].

However, little data are available on the molecular or genetic alterations associated with ovarian tumorigenesis. Given the existing understanding about the origin of ovarian cancer, the diagnosis and treatment of this malignancy remain major clinical challenges.

Aldehyde dehydrogenases (ALDHs) are a family of enzymes that are ubiquitous in nearly all mammalian tissues and catalyze the aldehyde oxidation to the carboxylic acid form [6]. ALDHs participate in various fundamental bioprocesses, such as proliferation, differentiation, survival, and oxidative stress [7]. To date, 17 ALDH isoforms have been identified, including ALDH1, a key member of the ALDH family and a common marker of cancer stem cells.

ALDH1 is involved in regulating cell differentiation [8, 9], proliferation and motility [8, 10], and achieves its regulation role in stem cells particularly through the retinoid signaling pathway. ALDH1 is a candidate biomarker for the metastasis and prognosis of pancreatic carcinoma, gastric carcinoma, lung cancer, ovarian cancer, and breast cancer. The ALDH1 expression level may be correlated with the metastasis and prognosis of epithelial ovarian cancer (EOC) [11-15].

However, the existing views regarding the role of ALDH1 expression in human ovarian cancer remain controversial. Some studies indicate high ALDH1 expression predicts poor outcome of ovarian cancer with higher tumor stage and lymph node metastasis [10, 16-18], while other studies show better correlation between high ALDH1 expression and cancer-specific survival in ovarian cancer [10, 19]. Therefore, a comprehensive analysis of the controversial findings is warranted. Here meta-analysis was performed on the existing relevant studies to investigate the relationships of ALDH1 expression with the clinicopathological characteristics and survival of EOC. This meta-analysis aimed to estimate the correlation of ALDH1 with prognostic prediction and provide evidence for effective strategies and further treatment of ovarian cancer.

Materials and methods

Search strategy

Two authors independently searched all relevant articles on PubMed, Embase, CNKI and Cochrane up to July 3, 2017 and using the terms "acetaldehyde dehydrogenase 1" or "ALDH1", and "ovarian carcinoma" or "ovarian cancer". The references in the articles and reviews were also screened to identify additional relevant articles. The titles and abstracts of potential references were carefully examined to exclude irrelevant studies. The remaining relevant articles were reviewed in depth.

Selection criteria

Inclusion criteria were: (a) focus on ovarian cancer; (b) description of a correlation between ALDH1 expression and clinicopathological parameters, and/or assessment of survival duration. Exclusion criteria were: (a) letter or review; (b) insufficient data to determine the hazard ratio (HR) and 95% confidence interval (CI) about ovarian cancer. The quality of each included study was assessed by the Newcastle-Ottawa Scale (NOS), which consists of three quality parameters of selection, comparability, and outcome assessment. An NOS score ≥ 5 indicates high quality.

Data extraction

All data were extracted by two reviewers independently. All relevant data were extracted from texts, tables, and figures in data forms, including author, year of publication, country, patient number, detection method, cutoff value, International Federation of Gynecology and Obstetrics (FIGO) stage, lymph node metastasis, tumor grade, tumor location in the ovary, and ALDH1 expression-related survival. HRs based on multivariable analyses other than univariate analyses were extracted in prior. If one study did not provide HR with 95% CI, it was calculated using Kaplan-Meier survival curves on Engauge Digitizer 4.1. Any disagreement between the two reviewers on a certain study was resolved by full discussion until a consensus was reached.

Statistical analysis

All calculations were performed on RevMan 5.3 (Nordic Cochrane center, Copenhagen, Denmark) and STATA 14.0 (Stata, USA). The association between high ALDH1 expression and clinicopathologic characteristics (e.g. FIGO stage, tumor grade, lymph node metastasis, tumor location in ovary, survival) was evaluated using the odds ratios (ORs) and 95% CIs. Results were combined as pooled HRs and 95% CIs. Heterogeneity among 9 studies was assessed with a forest plot, Q test, and the inconsistency statistic (I^2). In case of no significant heterogeneity among studies, the pooled HR/RRs of each study were calculated by a fixed-effects model with Mantel-Haenszel method. Otherwise, a random-effects model with Inverse Mantel-Haenszel method was adopted. The pooled HR/RRs of overall survival were calculated by a fixed-effects model with Inverse Variance method. All CIs had 2-sided probability coverage of 95%. $P < 0.05$ was considered significant.

Results

Search results and description of studies

A flow diagram of the selection process is depicted in **Figure 1**. Preliminary search returned 244 articles of interest, including 27 animal and/or cell experiments, which were excluded later. Then 132 duplicates, 13 reviews, 61 studies due to lack of relevant data or no relevance with ovarian cancer and ALDH1, and 2 studies without enough data for analysis were excluded. Finally, 9 Chinese or English articles involving 1823 patients from America,

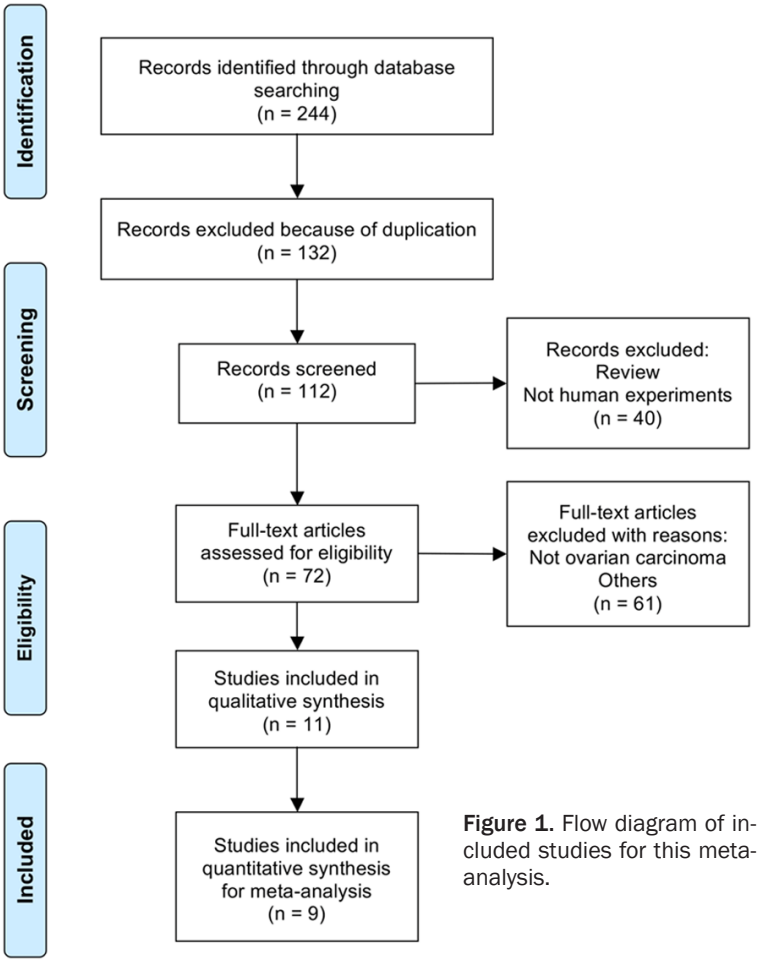


Figure 1. Flow diagram of included studies for this meta-analysis.

Norway, Germany or China were included in the meta-analysis. The sample sizes of these 9 articles varied from 80 to 442. ALDH1 expression was evaluated by immunohistochemistry in all articles. As for data analysis, 7 and 5 articles provided information for overall survival (OS) and disease-free survival (DFS), respectively. The characteristics of the included articles are shown in **Table 1**. The quality of all 9 studies ranged from 6 to 9, indicating all the included studies were of high quality.

Correlation between ALDH1 expression and clinicopathological parameters of ovarian cancer

Correlations between high ALDH1 expression and clinicopathological parameters in ovarian cancer patients from different races were analyzed, including Chinese and Caucasians. First, elevated ALDH1 expression was significantly correlated with the FIGO stage in both Chinese and Caucasians ($P < 0.00001$ and $P = 0.0001$, random-effects model, **Figure 2A**).

Then high ALDH1 expression versus low ALDH1 expression was significantly correlated with tumor grade of EOC in Chinese (pooled OR and 95% CI = 2.10 (1.20, 3.67); $P = 0.01$, random-effect model, **Figure 2B**). Finally, no significant association is found between ALDH1 over-expression and the lymph node metastasis of ovarian cancer (pooled OR and 95% CI = 2.47 (0.77, 7.87), $P = 0.13$, **Figure 2C**), or between ALDH1 upregulation and tumor location in the ovary (1.10 (0.62, 1.96), $P = 0.73$, **Figure 2D**).

Correlations between ALDH1 expression and subtypes of ovarian cancer

Interestingly, ALDH1 expression was significantly correlated with the main subtypes of EOC in different races (**Figure 3**). Furthermore, high ALDH1 expression was significantly correlated with both serous carcinoma (pooled OR and 95% CI = 0.37 (0.22, 0.62); random-effect model; $P = 0.0001$, **Figure 3A**) and mucinous carcinoma in Caucasians (6.82 (2.02, 23.05), $P = 0.002$, **Figure 3B**).

Additionally, positive ALDH1 expression is significantly associated with endometrioid carcinoma in Caucasians ($P = 0.003$), but with endometrioid carcinoma or clear cell carcinoma in Chinese (1.14 (0.56, 2.31), $P = 0.71$; 0.86 (0.41, 1.79), $P = 0.6805$, **Figure 3C**, **3D**).

ALDH1 expression and EOC survival outcome

OS outcomes of ovarian cancer with positive or negative ALDH1 expression from 6 studies involving 1383 patients were extracted and analyzed (**Figure 4A**). The random-effects model shows a significant association between ALDH1 over-expression and poor OS of EOC patients (HR = 1.59, 95% CI: [1.11, 2.29], $P =$

Table 1. Characteristics of included studies

NO	First author	Year	Country	Number	Hystopathological subtypes	Detection method	Antibody source	Cutoff value	FIGO Stage	Lymph node metastasis (Present/absent)	Grade (Well/Moderately and poorly)	Tumor location in ovary (Unilateral/Bilateral)	Methods of HR estimation	Survival	NOS score
1	Puxiang Chen	2015	China	80	40 Serous, 25 Mucinous, and 15 Clear cell	IHC	Santa Cruz Biotechnology	10%	I-IV	50/30	20/60	55/25	Given by author	OS	9
2	Ruixia Huang	2015	Norway	248	163 Serous carcinoma, 18 Mucinous carcinoma, 19 Endometrioid carcinoma, 11 Clear cell carcinoma, 11 Mixed epithelial tumor, 5 Undifferentiated tumor, 5 Unclassified tumor and 21 others	IHC	BD Transduction Laboratories	IRS score ≥ 7	I-IV	N/A	19/195	N/A	Given by author	OS, PFS	8
3	Catarina Liebscher	2013	Germany	131	high-grade serous ovarian carcinoma	IHC	BD Transduction Laboratories	IRS score ≥ 4	I-IV	67/39	14/117	N/A	Given by author	OS	6
4	Lan Yu	2017	China	207	159 Serous carcinoma, 28 Mucinous carcinoma, 13 Endometrioid carcinoma and 7 Clear cell carcinoma	IHC	Abcam -	IRS score ≥ 3	I-IV	a78/129	122/85	165/42	Given by author	OS	9
5	YuChi Wang	2012	China	84	61 Serous carcinoma, 14 Mucinous carcinoma, 3 Endometrioid carcinoma and 6 Clear cell carcinoma	IHC	BD Biosciences	50%	I-IV	N/A	13/71	N/A	Given by author	OS, PFS	8
6	Bin Chang	2009	USA	442	266 Serous carcinoma, 35 Endometrioid carcinoma, 5 Mucinous carcinoma, 14 Clear-cell carcinoma, 17 MMMT, 8 Poorly differentiated carcinoma, 6 Transitional cell carcinoma and 91 Mixed-type carcinoma	IHC	BD Biosciences	IRS score ≥ 2	I-IV	N/A	N/A	N/A	Survival curves	OS, PFS	7
7	Shan Deng	2010	USA	439	No given	IHC	BD Pharmingen	10%	N/A	N/A	N/A	N/A	Survival curves	OS, PFS	6
8	Hong Jing	2016	China	92	55 Serous carcinoma, 10 Mucinous carcinoma, 7 Endometrioid carcinoma, 6 Clear cell carcinoma and 14 Mixed adenocarcinoma	IHC	Assay biotech	IRS score ≥ 4	I-IV	17/75	14/78	N/A	N/A	N/A	7
9	Yanan Sun	2016	China	100	50 Serous carcinoma, 10 Mucinous carcinoma, 17 Endometrioid carcinoma and 23 others	IHC	Santa Cruz Biotechnology	IRS score ≥ 9	I-IV	67/33	15/85	N/A	Survival curves	PFS	7

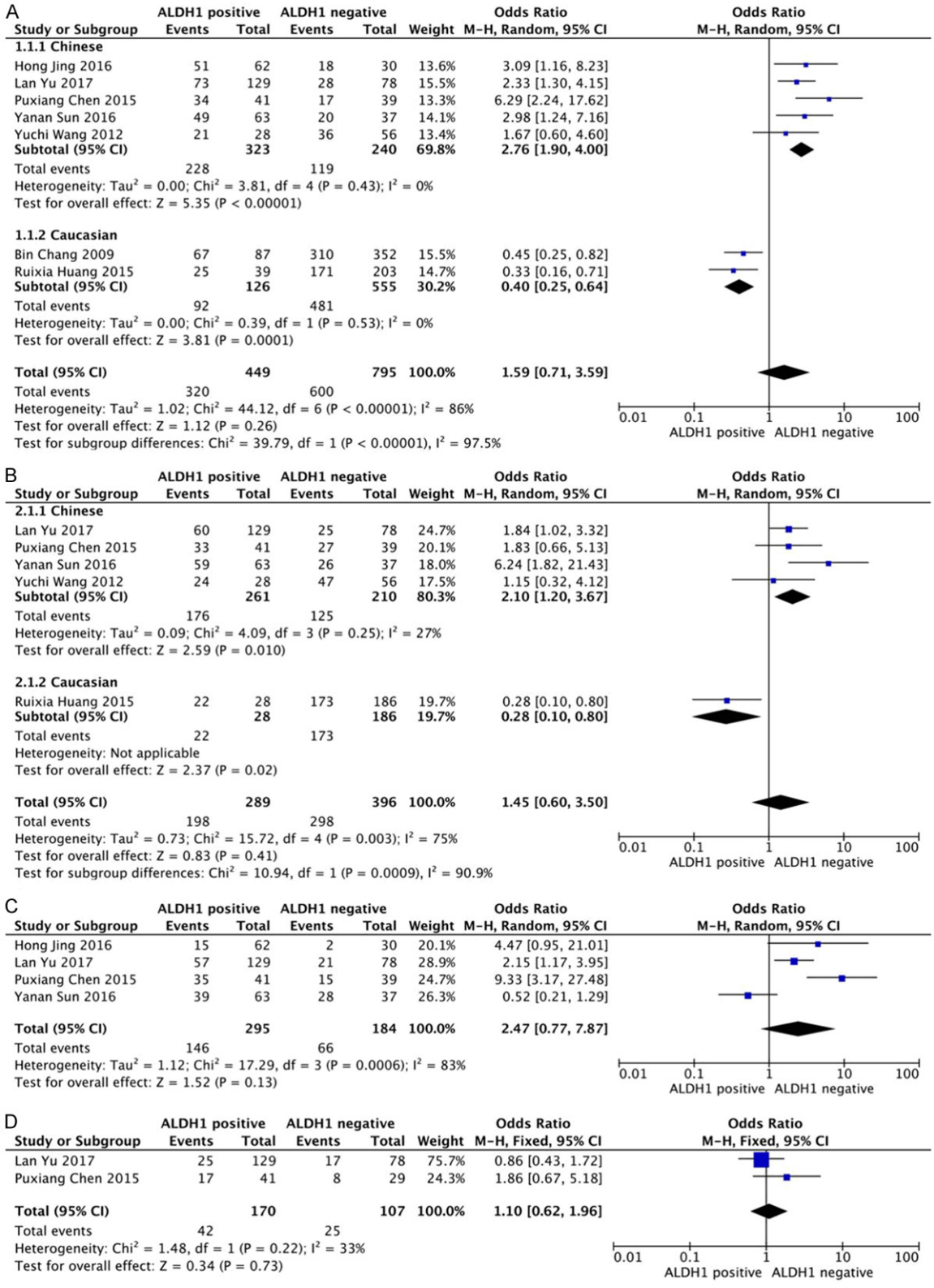
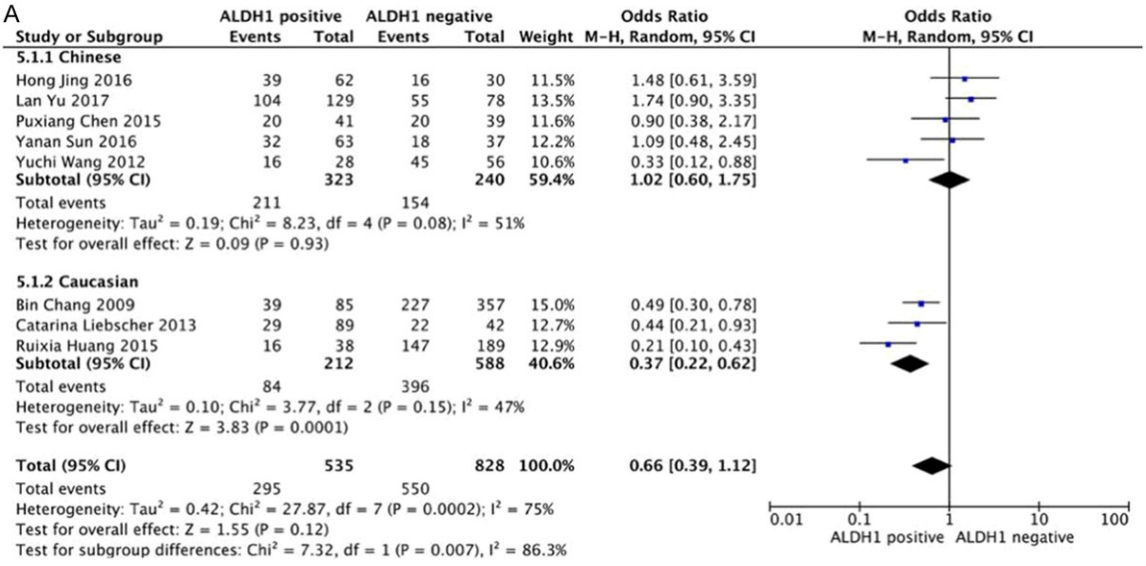


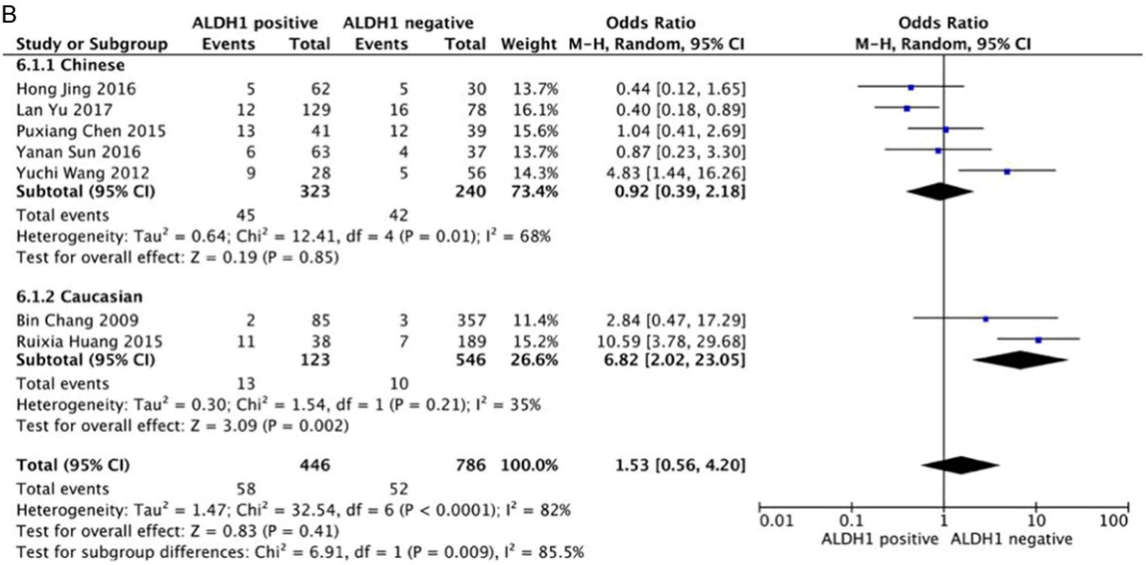
Figure 2. Forest plot of studies evaluating associations between high ALDH1 expression and clinicopathological parameters. A. FIGO stage. B. Tumor grade. C. Lymph node metastasis. D. Tumor location in ovary.

0.01), especially in Chinese ($P < 0.0001$). However, no significant relationship between high ALDH1 expression and progression-free survival (PFS) was found from 5 studies (pooled

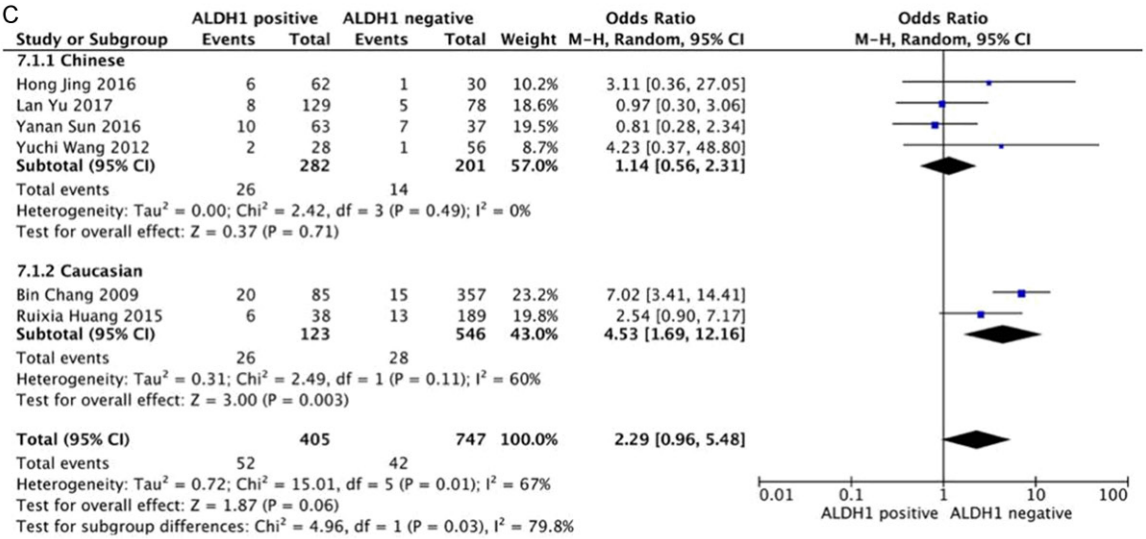
A


ALDH1 positive
ALDH1 negative
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
5.1.1 Chinese
Hong Jing 2016 39 62 16 30 11.5% 1.48 [0.61, 3.59]
Lan Yu 2017 104 129 55 78 13.5% 1.74 [0.90, 3.35]
Puxiang Chen 2015 20 41 20 39 11.6% 0.90 [0.38, 2.17]
Yanan Sun 2016 32 63 18 37 12.2% 1.09 [0.48, 2.45]
Yuchi Wang 2012 16 28 45 56 10.6% 0.33 [0.12, 0.88]
Subtotal (95% CI) 323 240 59.4% 1.02 [0.60, 1.75]
Total events 211 154
Heterogeneity: Tau² = 0.19; Chi² = 8.23, df = 4 (P = 0.08); I² = 51%
Test for overall effect: Z = 0.09 (P = 0.93)
5.1.2 Caucasian
Bin Chang 2009 39 85 227 357 15.0% 0.49 [0.30, 0.78]
Catarina Liebscher 2013 29 89 22 42 12.7% 0.44 [0.21, 0.93]
Ruixia Huang 2015 16 38 147 189 12.9% 0.21 [0.10, 0.43]
Subtotal (95% CI) 212 588 40.6% 0.37 [0.22, 0.62]
Total events 84 396
Heterogeneity: Tau² = 0.10; Chi² = 3.77, df = 2 (P = 0.15); I² = 47%
Test for overall effect: Z = 3.83 (P = 0.0001)
Total (95% CI) 535 828 100.0% 0.66 [0.39, 1.12]
Total events 295 550
Heterogeneity: Tau² = 0.42; Chi² = 27.87, df = 7 (P = 0.0002); I² = 75%
Test for overall effect: Z = 1.55 (P = 0.12)
Test for subgroup differences: Chi² = 7.32, df = 1 (P = 0.007), I² = 86.3%
0.01 0.1 1 10 100
ALDH1 positive ALDH1 negative

B


ALDH1 positive
ALDH1 negative
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
6.1.1 Chinese
Hong Jing 2016 5 62 5 30 13.7% 0.44 [0.12, 1.65]
Lan Yu 2017 12 129 16 78 16.1% 0.40 [0.18, 0.89]
Puxiang Chen 2015 13 41 12 39 15.6% 1.04 [0.41, 2.69]
Yanan Sun 2016 6 63 4 37 13.7% 0.87 [0.23, 3.30]
Yuchi Wang 2012 9 28 5 56 14.3% 4.83 [1.44, 16.26]
Subtotal (95% CI) 323 240 73.4% 0.92 [0.39, 2.18]
Total events 45 42
Heterogeneity: Tau² = 0.64; Chi² = 12.41, df = 4 (P = 0.01); I² = 68%
Test for overall effect: Z = 0.19 (P = 0.85)
6.1.2 Caucasian
Bin Chang 2009 2 85 3 357 11.4% 2.84 [0.47, 17.29]
Ruixia Huang 2015 11 38 7 189 15.2% 10.59 [3.78, 29.68]
Subtotal (95% CI) 123 546 26.6% 6.82 [2.02, 23.05]
Total events 13 10
Heterogeneity: Tau² = 0.30; Chi² = 1.54, df = 1 (P = 0.21); I² = 35%
Test for overall effect: Z = 3.09 (P = 0.002)
Total (95% CI) 446 786 100.0% 1.53 [0.56, 4.20]
Total events 58 52
Heterogeneity: Tau² = 1.47; Chi² = 32.54, df = 6 (P < 0.0001); I² = 82%
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Chi² = 6.91, df = 1 (P = 0.009), I² = 85.5%
0.01 0.1 1 10 100
ALDH1 positive ALDH1 negative

C


ALDH1 positive
ALDH1 negative
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
7.1.1 Chinese
Hong Jing 2016 6 62 1 30 10.2% 3.11 [0.36, 27.05]
Lan Yu 2017 8 129 5 78 18.6% 0.97 [0.30, 3.06]
Yanan Sun 2016 10 63 7 37 19.5% 0.81 [0.28, 2.34]
Yuchi Wang 2012 2 28 1 56 8.7% 4.23 [0.37, 48.80]
Subtotal (95% CI) 282 201 57.0% 1.14 [0.56, 2.31]
Total events 26 14
Heterogeneity: Tau² = 0.00; Chi² = 2.42, df = 3 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)
7.1.2 Caucasian
Bin Chang 2009 20 85 15 357 23.2% 7.02 [3.41, 14.41]
Ruixia Huang 2015 6 38 13 189 19.8% 2.54 [0.90, 7.17]
Subtotal (95% CI) 123 546 43.0% 4.53 [1.69, 12.16]
Total events 26 28
Heterogeneity: Tau² = 0.31; Chi² = 2.49, df = 1 (P = 0.11); I² = 60%
Test for overall effect: Z = 3.00 (P = 0.003)
Total (95% CI) 405 747 100.0% 2.29 [0.96, 5.48]
Total events 52 42
Heterogeneity: Tau² = 0.72; Chi² = 15.01, df = 5 (P = 0.01); I² = 67%
Test for overall effect: Z = 1.87 (P = 0.06)
Test for subgroup differences: Chi² = 4.96, df = 1 (P = 0.03), I² = 79.8%
0.01 0.1 1 10 100
ALDH1 positive ALDH1 negative

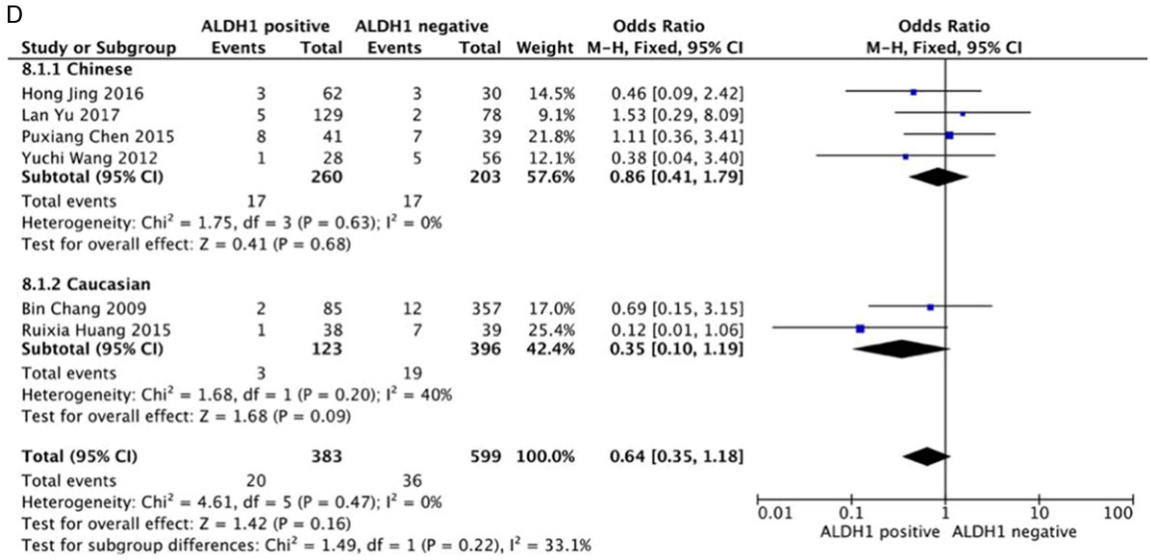


Figure 3. Forest plot of studies evaluating associations between high ALDH1 expression and types of ovarian cancer. A. Serous carcinoma. B. Mucinous carcinoma. C. Endometrioid carcinoma. D. Clear cell carcinoma.

HR = 1.14, 95% CI = 0.72-1.82, *P*= 0.57) in a random-effects model with heterogeneity (I^2 = 84%), suggesting high ALDH1 expression does not predict poor PFS among EOC patients (**Figure 4B**).

Publication bias

Funnel plot and Egger's test showed no publication bias of this meta-analysis or small-study effects between ALDH1 overexpression and OS in ovarian tumors (*P* = 0.210, **Figure 5**).

Discussion

Ovarian cancer is the leading cause of cancer-related death in women and is usually diagnosed at a late stage, but there is no highly effective targeted therapy so far. Moreover, the biological factors regulating ovarian cancer are among the least understood of all major human malignancies [20]. Thus, it is critical to identify biological/genetic markers associated with the pathophysiology and diagnosis of ovarian cancer.

ALDH1 is a detoxifying enzyme involved in the intracellular aldehyde oxidation in various cells. ALDH activity can be intensified in cancer stem cells of solid tumors, especially carcinomas. ALDH1 is considered as a common marker for both normal and malignant stem cells. ALDH1-positive cells reportedly possess the cancer stem cell properties in various cancers. Recently, the role and clinical significance of ALDH1 as an ovarian cancer stem cell marker have been explored [21]. Many studies suggest an elevated ALDH1 expression is associated with poor OS or PFS, while other studies suggest low ALDH1 is correlated with OS in ovarian cancer patients. Thus, the existing findings remain inconsistent, which can be reasonably addressed by meta-analyzing all available data from relevant studies. Under this background, 9 studies involving 1823 patients were meta-analyzed to assess whether ALDH1 was associated with prognosis of EOC. To the best of our knowledge, this is the largest and most comprehensive meta-analysis so far regarding the association between high ALDH1 expression and survival of EOC patients.

First, the correlation between high ALDH1 expression and clinicopathological characteristics (including FIGO stage, tumor grade, metastasis, tumor location in ovary, and tumor types) was analyzed comprehensively and showed no significant association. Then subgroup analysis showed ALDH1 expression dramatically differed between Chinese and Caucasians in clinic, and higher ALDH1 expression was associated with both FIGO stage and tumor grade in Chinese. Moreover, subgroup analyses based on subtypes of EOC showed serous carcinoma, mucinous carcinoma and endometrioid carci-

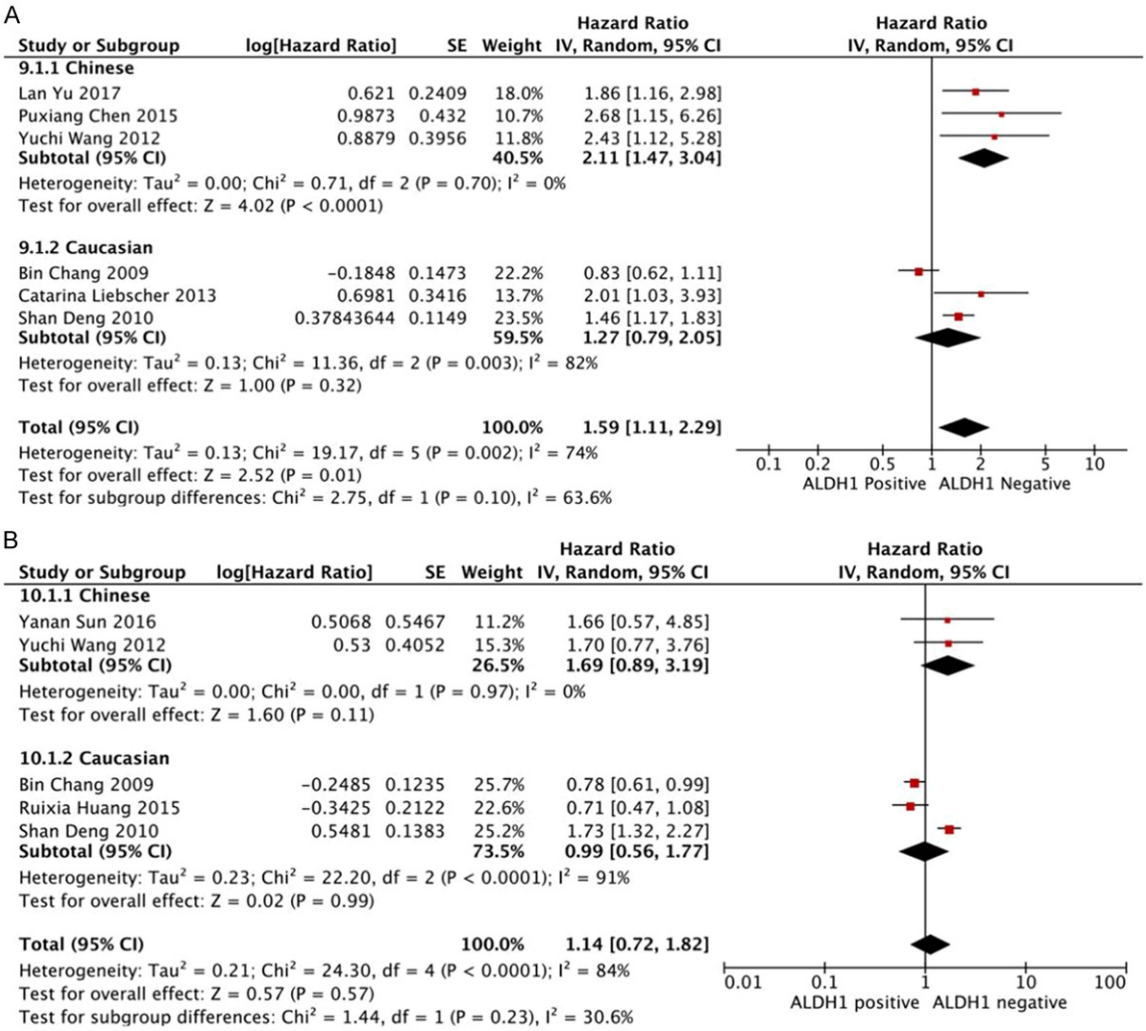


Figure 4. Forest plot of studies evaluating associations between high ALDH1 expression and survival of ovarian cancer. A. Overall survival. B. Progression-free survival.

noma were all correlated with ALDH1 expression in Caucasians. Therefore, our results indicate that ALDH1 has different meanings for Chinese and Caucasian races and ALDH1 could be a specific predictive maker for EOC in Asians and Europeans. Nevertheless, further mechanistic studies and large-scale experiments are needed to ascertain whether ALDH1 expression is associated with other clinicopathological characteristics of EOC. Furthermore, ovarian cancer patients with higher versus lower ALDH1 expression had significantly longer OS, indicating higher ALDH1 expression is correlated with poorer OS (HR: 1.59 (1.11, 2.29)), but not with PFS among EOC patients (1.14 (0.72, 1.82)). Sensitivity analysis showed no significant change in the corresponding pooled HRs, indicating our conclusion is reliable.

To the best of our knowledge, this is the first study to comprehensively summarize studies on the prognostic role of ALDH1 in EOC. The results indicate significant association between ALDH1 expression and several clinicpathological characteristics among Chinese and Caucasians. It is remarkably confirmed that EOC patients with ALDH1 over-expression tend to have a worse survival outcome in terms of OS.

However, this meta-analysis has several limitations. First, the criteria defining positive or negative ALDH1 expression, the criteria for calculating ALDH1 cut-off values, the source of antibody, concentration and evaluation method used are all inconsistent across the included studies. The definitions of outcome measures

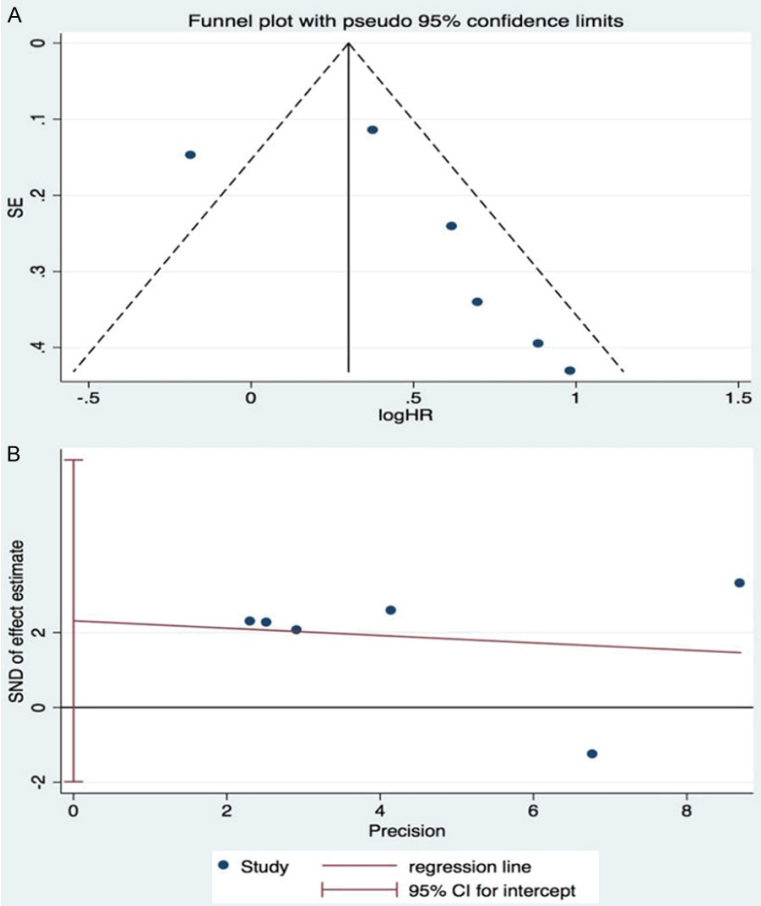


Figure 5. Funnel plot and Egger's test for publication bias in studies for OS and PFS in ovarian cancer. A. Funnel plot for OS. B. Egger's test for OS.

are unavailable in some studies. The different classifications and antibodies might have introduced obvious heterogeneity. Second, treatments other than surgery involved in the enrolled patients may increase the baseline heterogeneity. Third, studies were reported in non-English language only, unpublished studies, and conference abstracts were not included. Fourth, data from several studies were collected through survival curve reconstruction rather than directly, which inevitably led to the considerable bias.

Nevertheless, this comprehensive meta-analysis statistically confirms that (1) abnormally positive ALDH1 expression is significantly associated with clinicopathological characteristics and overall survival of ovarian cancer patients, (2) ALDH1 upregulation may act as an independent predictive and prognostic factor of ovarian cancer, and (3) ALDH1 can be a prognostic and predictive marker for poor prognosis of EOC.

In conclusion, existing evidence verified that positive ALDH1 expression is a negative predictor for survival in ovarian cancer. Nevertheless, more multicenter studies with larger sample size are needed to present more reliable evidences with clinical relevance and precise molecular explanation for the abnormal ALDH1 expression.

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Disclosure of conflict of interest

None.

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