RESEARCH COMMUNICATION

Association of Reduced Immunohistochemical Expression of E-cadherin with a Poor Ovarian Cancer Prognosis - Results of a Meta-analysis

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Abstract

Purpose: E-cadherin is a transmemberane protein which is responsible for adhesion of endothelial cells. The aim of our study was to assess existing evidence of associations between reduced expression of E-cadherin and prognosis of ovarian cancer with a discussion of potential approaches to exploiting any prognostic value for improved clinical management. Methods: We conducted a meta-analysis of 9 studies (n=915 patients) focusing on the correlation of reduced expression of E-cadherin with overall survival. Data were synthesized with random or fixed effect hazard ratios. Results: The studies were categorized by author/year, number of patients, FIGO stage, histology, cutoff value for E-cadherin positivity, and methods of hazard rations (HR) estimation, HR and its 95% confidence interval (CI). Combined hazard ratios suggested that reduced expression of E-cadherin positivity was associated with poor overall survival (OS), HR= 2.10, 95% CI:1.13-3.06. Conclusion: The overall survival of the E-cadherin negative group with ovarian cancer was significant poorer than the E-cadherin positive group. Upregulation of E-cadherin is an attractive therapeutic approach that could exert significant effects on clinical outcome of ovarian cancer.

Keywords: E-cadherin - overall survival - ovarian cancer - meta-analysis

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Introduction

Ovarian cancer is the leading cause of death in female reproductive system diseases which threaten women's health worldwide. While in early stage the patient merely complain pelvic uncomfortable and ignore them in crisis. Thus though we have revealed obvious development in surgical techniques and imaging method, we fail to make diagnosis in early stage and take intervention timely. On the other hand, prognosis associated with ovarian cancer is poor, five-year survival for all stages is 47% and less than 30% for advanced stages (Carter and Downs Jr, 2011). Histotype, FIGO stage and grade of differentiation are recognized as classical prognostic factors, but they are unsufficient to predict an individual patient's prognosis. Hence identification and validation of prognostic factors can help to evaluate prognosis of patients and may contribute to ovarian cancer screening and treatment.

E-cadherin (also named cadherin 1) is a epithelial subtype of cadherin which is named for calcium dependent adhesion. It is expressed predominantly in epithelial cells where regulate the histogenesis, stabilization and differentiation of epithelium (Berx and Roy, 2009). Normal E-cadherin expression plays an important role in tissue architecture and the maintenance of tissue integrity to control the growth and development of cells. Reduced expression of E-cadherin weaken the strength of cellular adhesion which result in increased cellular motility. As is known to all, cell and cell adhesiveness is generally decreased and leads to disruption of regular arrangement which promote cells crossing basement membrane and invade nearby tissues (Hirohashi and Kanai, 2003). Under the condition of tumor, E-cadherin can be simply understood as an adhesives to fix cells into established position. Up to now, large amount of studies confirmed that reduced expression of E-cadherin is correlated with gastrointestinal, breast, thyroid and ovarian cancers (Fluge et al., 2005; Altundag et al., 2006; Cisco et al., 2008; Yoshida et al., 2009). Further more, E-cadherin is also supposed to be used in diagnosis or prognosis. It is possible that E-cadherin could predict patient prognosis and this requires elucidation.

However, not all related studies showed consistent conclusions. Some studies suggested reduced expression of E-cadherin is significantly related with poor survival while some showed no relation between E-cadherin and survival rate in ovarian cancer. Thus we performed a meta-analysis of all available studies with inconclusive results to observe whether E-cadherin is a prognostic factor for ovarian cancer. The aim of our study is to verify the hypothesis that reduced expression of E-cadherin would have a negative effect on overall survival.

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Materials and Methods

Search strategy

We performed an Electronic databases which included Medline, EMBASE and Sciencedirect to identify all related articles about E-cadherin and ovarian cancer. Published time was limitted between 1990 and February 1st, 2012. MESH words were designed as 'ovarian neoplasm' and 'cadherin 1'. At the same time, we screened references from eligible articles as well as reviews and editorials. If more than one study was published by the same medical center, we chosen the journal with higher influence factor or the larger sample size.

Selection criteria

We established included criteria as follow : (1) E-cadherin was assessed by immunohistochemistry (IHC). (2) The endpoints of investigation should include overall survival. (3) Log-Hazard ratio (HR) and its 95%CI were reported, or standard error (s.e.) and HR were given, or logrank X^2, survival curve and P value (Numerical value) were given. (4) All observed patients must be diagnosed as ovarian cancer by pathology. (5) Study population was divided into E-cadherin negative and positive group for survival analysis. Studies should be excluded: (1) the same author or the same medical center with duplicate data, the article with higher influence factor was chosen. (2) Follow-up was less than 2 year. (3) Non-original articles or borderline ovarian neoplasm. (4) Animal studies focused on subjects such as rabbit, BALB/c mouse, pig, and sheep. Two authors independently evaluated title and abstracts of all studies (n=384) to decide whether full-text should be screened further. Disagreement was resolved by discussing quality assessment and data collection between us. We examined 64 full-texts and pick up information with included and excluded criteria.

Data extraction and analysis

Data were extracted according to standardized form which included the necessary information : author/year, number of patients, FIGO stage, histology, cutoff value for E-cadherin positivity, methods of detection, types of survival analysis, and methods of HR estimation, HR and its 95% confidence interval (CI).

Hazard ratio (HR) is a definition of both time to event and censoring, and it is recommended for prognostic meta analysis. For some studies which didn't report HR and 95%CI of univariate analysis directly, we need to obtain data from survival curves. Survival curve could be read by Engauge Digitizer (version 4.1) which is downloaded from http://sourceforge.net. All the calculation methods were derived from PARMAR (Parma et al., 1998).

1. For the situation, HR and P value were provided by original study, but logrank X^2 and 95% CI of HR was missing. The first step was to calculate logrank X with excel using Function "CHIDIST", deg_freedom was "1". Next step, se var((ln(HRi))= $\sqrt{\frac{\ln(HRi)}{(logrank\ X2)^{1/2}}}$. Last step, RevMan 5.1 was used to obtain HR and 95%CI.

2. For the situation, survival curve and P value were provided by original study, but HR and 95% CI were missing. HR could be obtained as follow: HR= $\frac{Ori/Eri}{Oci/Eci}$. Ori=observed number of events in the E-cadherin positive group; Oci=observed number of events in E-cadherin negative group; Eri=logrank expected number of events in the E-cadherin negative group; Eci=logrank expected number of events in the E-cadherin positive group. Then HR and its 95% CI could be calculated in accordance with the above method.

3. For the situation, survival curve and 95%CI of HR were provided by original study, but HR and logrank X^2 were missing. HR= $\frac{Ori/Eri}{Oci/Eci}$, se var ((ln(HRi))= $\sqrt{\frac{upperCIi-lowCIi}{2\int^{-1}(1-\frac{\alpha i}{2})}}$. subsequently, RevMan 5.1 was used to obtain HR and its 95%CI.

For every single study, the survival analysis between E-cadherin positive group and negative group was considered significant when the P-value was < 0.05 in two-tailed test (univariate analysis). We marked the results as 'positive' when E-cadherin negative predicted poorer OS, DFS, and PFS. Conversely, results were marked as 'negative'. In the sake for quantitative aggregation of OS, DFS and PFS, we measured the E-cadherin on survival by combining HR and its 95%CI which was first published by Peto .

Between-study heterogeneity was assessed by Chi-square test and expressed by I^2 index. When $I^2 > 35\%$, we considered it as heterogeneity, and random effect (I-V heterogeneity) was used. When $I^2 \leq 35\%$, fixed effect was used. We considered a worse survival when observed HR>1 for E-cadherin negative group, which Martin et al. and Barraclough et al. reported respectively (Martin et al., 2004; Barraclough et al., 2011). This impact of E-cadherin negative on OS, DFS, and PFS was considered with statistical significance if the combined HR and its 95% CI didn't overlap 1.

Begg's, Egger's Test and contour-enhanced funnel plot (presented by STATA 12.0) were used to identify the possibility of publication bias. We considered probable significant publication bias when $p < 0.05$. Furthermore, contour-enhanced funnel plot has the function to indicate regions of statistical significance. And contour overlay help to interpret funnel plot and identify whether the cause of asymmetry is due to factors such as variable study quality.

Results

Study characteristic

In totally, 384 relevant citations were retrieved after taking search strategy. We read 384 titles and abstracts of which 291 were irrelevant and 29 review articles on E-cadherin expression of ovarian cancer, following deduplication, two reviewers completed this work independently. Subsequently, 64 studies of full-text were read for detail, there were 19 studies were included. Finally, 9 studies (n=915) fulfilled and the main features were summarized and shown in Table 1. Of the 9 ovarian cancer studies (Chen et al., 1999; Faleiro-Rodrigues et al., 2004; Cho et al., 2006; Giatromanolaki et al., 2006; Voutilainen et al., 2006; Blechschmidt et al., 2008; Shim et al., 2009; Ho et al., 2010; Dian et al., 2011; Huang and Sui, 2012), all the studies dealt with survival analysis by overall survival .

Table 1. Main Characteristic of 9 Included Studies

Author (year-country)	No.	Figo stage	Histology	Cutoff vaule	Survival	HR estimation	HR(95%CI)	conclusion
Blechschmidt/2006 (2008-Germany)	48	III:37,IV:11	serous:37,other:11	10%	OS	Given by author	2.82(1.3,6.3)	positive
Cho (2006-Korea)	95	NC	Serous:95	10%	OS	Survival curves	1.23(1.12,1.8)	positive
Darai (1997-France)s	20	I+II:6,III+IV:14	serous:10,mucinous:10	10%	OS	Survival curves	1.22(1.01,1.42)	positive
Dian (2011-Germany)	100	I+II:15,III+IV:85	serous:100	25%	OS,PFS	survival curves	1.68(0.51,2.85)	negative
Faleiro-Rodrigues (2004-Portugal)	104	I+II:38,III+IV:66	serous:104	10%	OS	given by author	4.83(1.38,16.9)	positive
Ho (2010-Taipei,China)	58	II:5,III+IV:53	NC	10%	PFS,OS	given by author	PFS:1.45(0.75,2.95) OS:2.30(1.10,4.81)	positive
Huang (2012-China)	136	NC	epithelial	5%	OS	given by author	1.15(0.63,2.09)	negative
Shim (2009-Korea)	72	II:11,III+IV:61	serous:72	25%	OS	Survival curves	1.82(1.32,2.86)	positive
Voutilaninen (2006-Finland)	282	I+II:121,III+IV:161	Epithelial:132,other:150	5%	OS	survival curves	1.70(0.71,2.69)	negative

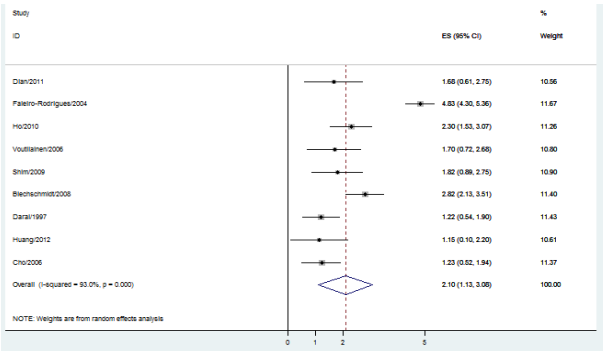

Figure 1. The Association Between Reduced Expression of E-cadherin and Overall Survival of Ovarian Cancer Stratified by HR Estimation. Meta-analysis of 9 eligible studies evaluating E-cadherin in overall survival. HR and its 95% CI for OS is 2.10 (1.13-3.06)

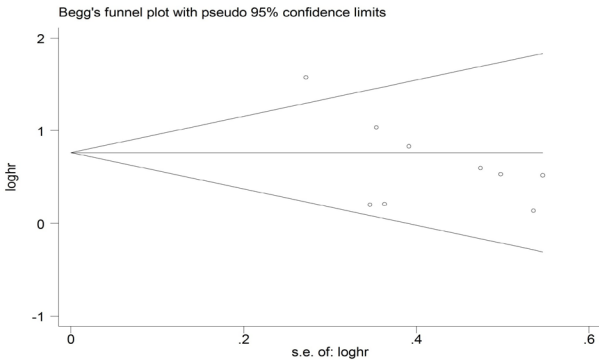

Figure 2. Funnel plots of Begg's was Used to Evaluate Publication Bias on Overall Estimate. Studies is symmetrically distributed which suggest lack of publication bias

Of the 9 eligible studies for the meta-analysis, HR estimation of 4 studies was given by authors, while 5 were calculated by survival curves (The formula was seen in Methods). FIGO stage of study population was mainly focused on stage III and IV which accounts for 448 (65.5%) (exclude the two studies which the FIGO stage were not clear). Study results were shown in Table 1, six of 9 studies using overall survival were "positive" which indicated E-cadherin expression was a poor prognostic factor in ovarian cancer, while 2 studies progression-free survival were "negative" which indicated no relation of

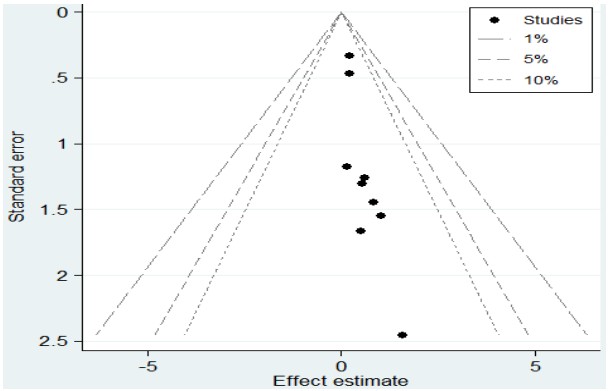

Figure 3. Contour-enhanced Funnel Plot of 9 Eligible Studies Assessing the Influence of Reduced Expression of E-cadherin Positivity in OS of Ovarian Cancer Patients

E-cadherin expression and PFS.

Meta-analysis

We analyzed HR value of overall survival between E-cadherin positive and negative group. Test of heterogeneity shown that chi-squared=8.16, I2=93.0% >30%, hence random model was chosen. There was significant difference between two groups(HR=2.10,95% CI:1.13-3.06) , E-cadherin negativity was associated with poor overall survival which its 95% CI is overlapped with 1 (Figure 1).

Publication bias

In order to assess the publication bias of meta-analysis, Begg's and Egger's test were performed. Nine studies evaluating overall survival of patients with ovarian cancer yielded a Begg's and Egger's test which p=0.466 and p=0.08 respectively, Begg's funnel plot is shown (Figure 2) . At the same time, confunnel plot (contour-enhanced funnel plot) was undertaken which also indicates absence of publication (Figure 3).

Discussion

The present systematic review and meta-analysis shows that the reduced expression of E-cadherin in

ovarian cancer is a poor prognostic factor with statistical significance for overall survival (HR=2.10,95% CI:1.13-3.06), but not clear for progression-free survival caused by lack of sufficient data. Up to now, overall survival is the most wildly used endpoint in oncology trails (Oza et al., 2011). Publication bias is absent in our analysis which is detected by Begg's, Egger's test and confunnel plot. We thought reduced E-cadherin expression may be a strong and important prognostic factor in ovarian cancer. Study populations are concentrated in the advanced ovarian cancer which defined as FIGO stage III and IV ,Therefore the conclusion may be more suitable for advanced ovarian cancer.

E-cadherin contributed to overall survival can be rationalized by the following mechanisms. Firstly, EMT was considered to be a core hallmark of cancer metastasis which referred to a series of programmes including lost epithelial properties like cell-cell adhesion, planar and apical-basal polarity, exhibited mesenchymal phenotypes such as invasiveness, heightened resistance to apoptosis (21), and possessed of stem-cell like characteristic. E-cadherin bind with β-catanin located on cyto-membrane under normal condition, while reduced E-cadherin enabled β-catanin to translocate to nucleus where it served as a transcription factor to activate EMT by Wnt signaling pathway which eventually promoted formation of distant tumor metastases (Vincan and Barker, 2008). Janda E et al demonstrated degradation of E-cadherin was a critical event for early phases of Raf and TGF-β-dependent EMT which was mediated by endosome and lysosome, subsequently, transcriptional downregulation promoted late process of EMT (Janda et al., 2006).

Then, E-cadherin was responsible for tumor cell growth suppression. It was well known that the inappropriately activated PI3K-Akt signaling pathway played a pivotal role in tumorigenesis. Activated PI3K and Akt initiated a series of signal transduction cascade that promoted cancer cell growth, survival and metabolism. Moreover, by activating mTOR complex 1, the major downstream effectors of PI3K-Akt signaling pathway, increased the cellular metabolic activities and biosynthesis (Engelman, 2009). Recently studies demonstrated that reduced expression of E-cadherin results in dysregulation of PI3K/Akt signaling by upregulating PTEN expression via β-catenin-mediated Egr1 regulation. Together, the relationship between reduced E-cadherin and deregulated of PI3K/Akt signaling indicated the function of E-cadherin in regulating metabolic and proliferation signal pathways (Lau et al., 2011). Meanwhile, St Croix et al. (1998) found E-cadherin inhibited proliferation by upregulation of cyclin-dependent kinase inhibitor p27 and down-regulation the activity of mitogenic pathways such as EGFR, which also indicated its function in cell growth regulation.

Additionally, EMT transcription factors such as snail and slug were also found to be associated with cisplatin resistance in ovarian cancer (Haslehurst et al., 2012) as well as in breast cancer (Yu et al., 2007), indicated the importance of E-cadherin EMT in therapeutic resistance.

There were several clinical significances in our study. First of all, reduced expression of E-cadherin could serve as an indicator for identifying clinico-pathological characteristics including ovarian cancer stage and metastatic potential. Recent studies suggested there were a negative correlations between E-cadherin expression and differentiation, lymph metastasis (Yuecheng et al., 2006; Yamamoto et al., 2007).

Secondly, E-cadherin was competent act as a potential marker for ovary cancer diagnosis in clinic. Gadducci et al confirmed that ovarian cancer presented higher level of E-cadherin in serum than ovary benign neoplasm (Gadducci et al., 1999). Perl et al found that persistent expression of E-cadherin on Rip1Tag2 mice stagnated at adenoma stage, whereas dominant-negative E-cadherin expression induced early invasion, and they concluded E-cadherin was one rate-limiting step in the evolvement of adenoma to adenocarcinoma (Perl et al., 1998). Taking these into consideration, E-cadherin may be a biomarker in discriminating benign and malignant tumors.

Lastly, E-cadherin could be a therapeutic target and a tool for assessing treatment responses. By blocking E-cadherin in vivo and vitro, Sawada et al. (2008) found that α5-integrin was upregulated through activation of epidermal growth factor pathway. Further, they treated SKOV-3ip ovarian cancer xenografts with α5β1-integrin antibody, ascites and metastases were largely decreased. E-cadherin/catenin complex may as a potential target for anti-cancer therapy due to its multifactorial regulation between different signaling pathways such as wnt signaling, notch signaling ,TGF-β signaling pathway and their effector regulators. Independently of these observations, Mareel et al (1996) reported that insulin-like growth facor-1 and tamoxifen can upregulate E-cadherin/catenin complex as well as reduce invasiveness. Taken all-above together, E-cadherin and its epigenetic and transcriptional regulators could be a promising target for ovarian cancer therapy.

We should take note of the difference in definition of E-cadherin positivity. Unfortunately, not all eligible studies taken the same standard, cut off value varies from 5% to 25% and most studies were 10% (five studies). There were only two studies (Cho et al., 2006; Dian et al., 2011) provided progression free survival (PFS) information, we couldn't obtain meta results because of its insufficient original data. Furthermore, HR values and its 95% CI were obtained by manual calculation which induce inevitable errors. Besides, the editors preferred to receive articles with positive experimental results, leading to publication bias which resulting in data missing. Therefore, we urgently need high-quality data to draw more reliable conclusions.

In conclusion, our meta-analysis of association between reduced E-cadherin expression and overall survival among patients with ovarian cancer suggests that reduced E-cadherin may be associated with lower overall survival rate. As mentioned, owing to the clinical importance of E-cad, upregulation of E-cadherin is an attractive therapeutic approach that could show significant effect on clinical outcome of ovarian cancer. In order to reduce systemic error in the future studies, we recommend standardization of E-cadherin positivity cutoff value and give HR value and its 95% CI. Our results should be

confirmed by more comprehensive investigations with large population.

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