RESEARCH ARTICLE

Roles of E-cadherin and Cyclooxygenase Enzymes in Predicting Different Survival Patterns of Optimally Cytoreduced Serous Ovarian Cancer Patients

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Abstract

The relation between cyclooxygenase enzymes and E-cadherin, along with the roles of these markers in the prediction of survival in optimally cytoreduced serous ovarian cancer patients was investigated. Individuals who underwent primary staging surgery and achieved optimal cytoreduction (largest residual tumor volume <1 cm) constituted the study population. Specimens of 32 cases were immunohistochemically examined for cyclooxygenase-1, cyclooxygenase-2, and E-cadherin. Two could not be evaluated for E-cadherin and cyclooxygenase-1. Overall, 14/30, 19/30, and 15/32 cases were positive for E-cadherin, cyclooxygenase-1, and cyclooxygenase-2, respectively. The expressions of E-cadherin and cyclooxygenase-2 were inversely correlated (p:0.02). E-cadherin expression was related with favorable survival (p<0.001). The relation between the expression of cyclooxygenase enzymes and poor survival did not reach statistical significance. On multivariate analysis, E-cadherin appeared as an independent prognostic factor for survival. In conclusion, E-cadherin expression is strongly linked with favorable survival. E-cadherin and cyclooxygenase 2 may interact with each other during the carcinogenesis-invasion process. Further studies clarifying the relation between E-cadherin and cyclooxygenase enzymes may lead to new preventive and therapeutic targets in ovarian cancer.

Keywords: Cyclooxygenase - E-cadherin - ovarian cancer - survival

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Introduction

Studies have shown that cyclooxygenase (Cox) enzymes and E-cadherin have roles in ovarian cancer like many other cancers (Ali-Fehmi et al., 2005; Zahou et al., 2007). E-cadherin is expressed in epithelial cells and participates their differentiated functions and intercellular adhesion. Reduction or loss of E-cadherin expression represents transition from epithelial to mesothelial characteristics (Faleiro-Rodrigues et el., 2004; Brouxhon et al., 2007), which may be a step in carcinogenesis, invasion, or metastasis. On the contrary, increased Cox expression accompanies carcinogenesis and increased invasion (Gupta et al., 2003; Ali-Fehm et al., 2005).

Based on their previously defined roles in carcinogenesis, the relation of E-cadherin and Cox enzymes in terms of carcinogenesis and invasion has been suggested in many cancers such as the lungs, bladder, kidneys, gastric, and colon (Chen et al., 2004; Jang et al.,2009). Cox-2 inhibition leads to increase E-cadherin expression and this relation was suggested as the target of newly developed therapies (Chen et al., 2004; Rao et al., 2006; Okamato et al., 2008; Jang et al.,2009). Despite these studies performed on other cancers, roles of these markers in ovarian cancer survival remain unclear and the relations among expression patterns of these 3 markers and their ability to predict survival have not been investigated.

In this study, expression of Cox-1, Cox-2, and E-cadherin and the roles of these 3 markers in the prediction of survival were analyzed in patients with serous papillary ovarian cancer following optimal cytoreduction.

Materials and Methods

Patients diagnosed with epithelial ovarian cancer were identified from patient files. A series of 32 ovarian serous carcinoma cases who underwent primary staging surgery and achieved optimal cytoreduction (largest residual tumor volume <1 cm) without previous chemotherapy were selected among these cases. The reason why patients with optimal cytoreduction were chosen was to eliminate the effect of this important prognostic factor on the survival analyses. This study was approved by the Ethics Committee of our institution.

Immunohistochemistry

In all patients, formalin-fixed and paraffin-embedded

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tumor tissue was available. For each case, two samples of core biopsies representing the tumor in 2 mm diameter were taken from the paraffin blocks and used for the preparation of tissue microarray blocks. Immunohistochemistry was applied to 4 μm sections of tissue array blocks. Sections were mounted on Poly-D lysine (Sigma) coated slides and deparaffinized, while antigen retrieval was performed by citrate buffer (pH 6.0). We carried out immunohistochemical staining with automatic immunostainer (Ventana Benchmarc, NexES IHC, Tucson, USA). Immunohistochemical staining of Cox-1 (Mouse anti-Cox-1, clone Cox111, 1:100 dilution, Zymed, San Francisco, CA), Cox-2 (clone Cox229, 1:100 dilution; Zymed, San Francisco, CA), and E-cadherin (Mouse anti E-cadherin, clone 4A2c7, 1:100 dilution, Zymed, San Francisco, CA) were performed by applying the avidin–biotin peroxidase complex method. Due to intense base staining, two cases were not appropriately assessed for E-cadherin and Cox-1 and excluded from statically analysis. To ensure accurate and reproducible staining, normal intestine epithelium was used as a positive control. Normal intestine epithelium without the primary antibody was used as a negative control.

Scoring

Two pathologists (E.E. and A.S.), who were unaware of the clinical data or the disease outcome, examined all slides independently. The concordance rate was 97% between the 2 pathologists. In case of disagreement, slides were reevaluated for a final decision using a conference microscope.

Cox-1 and Cox-2 were scored according to cytoplasm staining. Strong membranous and cytoplasmic staining was considered a positive result for E-cadherin. Staining intensity was scored as 0 (negative), 1 (weak), 2 (medium), or 3 (strong). Stained cells being 0% was defined as 0, <1-25% as 1, 25-75% as 2, and >75% as 3. A combined score based on the multiplication of staining intensity and the percentage of stained cells was used as the final score as described previously (Shim HS et al., 2009). The multiplied staining intensity (0, 1, 2, 3) and stained cell percent (0, 1, 2, 3) was accepted as negative (0) if the result was 3≥ and positive (1) if the result was >3 (Figure 1).

Statistics

Statistical analyses were performed by SPSS 11.5. The correlation analysis was used to examine the associations of E-cadherin, Cox-1, and Cox-2 with each other and also with age, preoperative CA-125, ascites volume, and grade. Overall survival and progression free survival was estimated by Kaplan-Meier survival analysis. The log-rank test was used to compare survival estimates between subgroups. A p value <0.05 was considered as statistically significant. In order to identify independent prognostic factors, the multivariate Cox proportional hazards regression model was used for E-cadherin, Cox-1, and Cox-2 and their combinations. The entry and removal criteria used were p values of 0.10 for entry and p values of 0.20 for variable removal in Cox's regression analysis.

Results

The mean (±standard deviation: SD) age of patients at the time of surgery was 58.63 (±12.59) years, with a range of 22-82 years old. Patients' characteristics were shown in Table 1. Following surgery, all patients were given at least 6 cycles of paclitaxel and carboplatin combination.

The mean follow-up period was 33.7 (8-124) months and after this time, 37.5% (n=12) of patients were alive while 62.5% (n=20) had died. In 87.5% (n=28) of patients, the disease had recurred at a mean of 11.6 (3-31) months. Median overall survival (OS) was 34 months [±4.792 (95%CI, 24.6-43.3)]. In all patients, the estimated 5-years OS rate was 23.4%, while estimated 5-years progression-

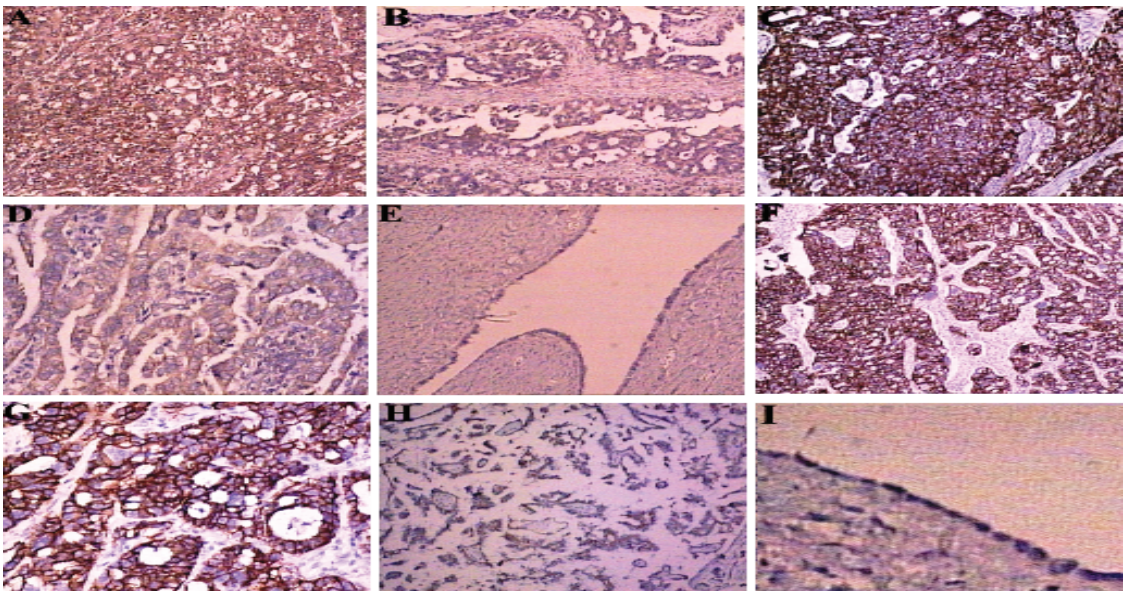

Figure 1. Immunoreactivity of Cox-1 (A, B), Cox-2 (C-E) and E-cadherin (F-I) Observed in Primary Serous Ovarian Carcinomas. A. Strong positivity for Cox-1 (x200). B. Weak immunreactivity for Cox-1 (x200). C. Immunohistochemistry staining for Cox-2 showing strong positivity (x200) D. Weak immunoreactivity for Cox-2 (x400) E. Negative expression of Cox-2 (x200) F. Strong positivity for E-cadherin (x100) G. Strong immunohistochemical staining for membranous E-cadherin (x400) H. Weak immunoreactivity for E-cadherin (x200) I. Negative expression of E-cadherin (x400)

Table 1. Patient Characteristics (n:32)

Age (years)		58.63±12.59 (22-82)
Stage (n):	II	5
	III	27
Grade (n):	I	4
	II	15
	III	13
Ascites volume (ml)		2218±1811 (0-6000)
CA-125 (IU/ml)		1028±1780 (5-7600)

*Values are mean±standard deviation (range). SD: standard deviation

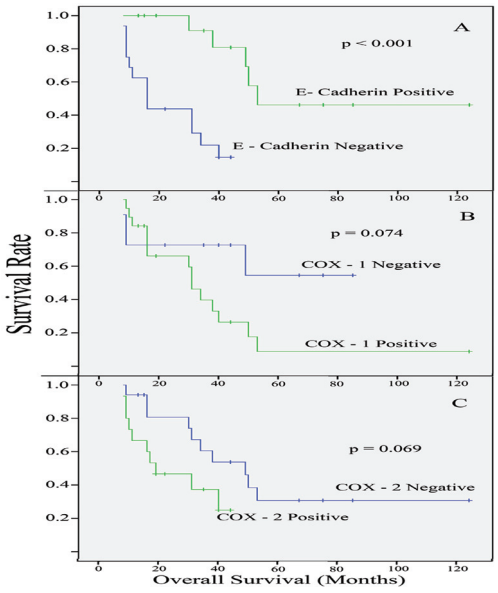

Figure 2. Relation of E cadherin. (A), Cox 1 (B) and Cox 2 (C) expressions with survival

free survival (PFS) rate was calculated as 10.9%.

E-cadherin scoring was negative in 16 and positive in 14 patients. The E-cadherin staining could not be evaluated in 2 patients with stage II disease. The positive E-cadherin results were significantly related with overall survival (p<0.001) (Figure 2A). However, PFS was not significantly related with E-cadherin (p=0.064).

Cox-1 scoring was negative in 11 and positive in 19 patients. Cox-1 was not assessed in the 2 patients in whom E-cadherin could not be evaluated. Although the survival was worse in patients with positive Cox-1, the difference was not statistically significant (p values 0.074 and 0.056 for OS and PFS, respectively) (Figure 2B).

Cox-2 scoring revealed negative results in 17 patients, while being positive in 15 patients. As seen in Cox-1, although worse survival associated positive Cox-2, this relation was not statistically significant (p values 0.069 and 0.193 for OS and PFS, respectively) (Figure 2C).

When the association of E-cadherin expression with Cox-1 and Cox-2 expressions were examined, E-cadherin was not related with Cox-1 (r=0.018; p=0.923), however; an inverse correlation was established between E-cadherin and Cox-2 (r=-0.412; p:0.023). Negative Cox-2 in case of positive E-cadherin (78.6%) and positive Cox-2 in case of negative E-cadherin (62.5%) was observed at high rates.

Grade 1, 2, or 3 disease did not affect OS (p: 0.947) and PFS (p: 0.440). A total of 27 patients had stage IIIC disease. Only 5 patients were stage IIB. Although the distribution was not suitable for analyses, stage did not affect OS and PFS.

Table 2. Survival Prediction Model

Variable	-2LogLikelihood	-2LogLikelihood Difference	Significance
Cox 1	101.001	97.672	3.329	0.09
Cox 2	114.435	111.365	3.07	0.083
E-cadherin	101.001	87.436	13.565	0.003
Cox 1+E-cadherin	101.001	84.478	16.523	<0.001
Cox 2+E-cadherin	101.001	87.4	13.601	0.001
Cox 1+Cox 2+E-cadherin	101.001	84.449	16.553	0.001

*E-cadherin Created the Maximum Difference whereas Addition of Cox 1 to E-cadherin Further Increases this Difference. [a]Prior, [b]after the selected variable added to the model

When the relations of E-cadherin, Cox-1, and Cox-2 expressions with age, preoperative CA-125, ascites volume, and grade were evaluated, only E-cadherin was found to be inversely correlated with ascites volume (r=-0.468, p:0.009).

We evaluated the effects of these 3 markers on the prediction of survival according to a survival prediction model. Table 2 summarizes the differences created by each marker and their various combinations on basal prediction model. Among these 3 markers, E-cadherin created the maximum difference whereas addition of Cox-1 to E-cadherin further increases this difference. E-cadherin and Cox-1 were found to have an impact on survival (Hazard ratio [HR]: 9.6 (95.0%CI: 2.1-43.6); p=0.003 for E-cadherin and HR: 2.5 (95%CI: 0.814-7.948; p=0.108 for Cox-1).

Discussion

E-cadherin, an adhesion molecule, was shown to participate carcinogenesis and invasion in many epithelial cancers (Cho et al., 2006; Shim et al., 2009). It has been shown a close link between the E-cadherin gene (CDH1) methylation and reduction in E-cadherin protein expression in human ovarian cancer (Rathi et al., 2002; Makarla et al., 2005). Furthermore 5-Aza treatment was found helpful in restoring functional E-cadherin expression and decreasing cell invasion (Yuechang et al., 2006). Also, in a recent study (Wang et al., 2011), E-cadherin expression via activation of the PI3K pathway in ovarian cancer cells has been suggested as a new strategy for cancer prevention and therapy.

Studies considering Cox-carcinogenesis relation have demonstrated that in ovarian cancer, Cox-2 is more strongly related to tumor invasion and metastasis than Cox-1 (Denkert and Kobel, 2002; Ali-Fehmi et al., 2005; Voutilainen et al., 2006). Expression of Cox 2 is associated with vascular endothelial growth factor (VEGF) expression, which contributes to tumor angiogenesis in ovarian cancer (Menczer, 2009) via loss of tumor suppressor genes such as p53 and SMAD4 and amplification of HER-2/neu oncogene (Lee et al., 2006; Erkinheimo et al., 2009). Several population-based studies have reported decrease in the risk of developing ovarian cancers with the consumption of several Cox inhibitors (Harris et al., 2005). Many trials performed in vivo or in vitro have also suggested the chemopreventative effect of various Cox inhibitors (Sun et al., 2006; Li et al., 2011).

The molecular mechanisms underlying this anticancer effect are not fully elucidated. However, in a recent study (Uddin et al., 2010) inhibition of Cox-2 activity using either specific (NS 398) or nonspecific Cox-inhibitor (aspirin) resulted in down regulation of Cox-2, inactivation of AKT as well as its downstream target Foxo1/FKHRL1. Furthermore, these findings support the hypothesis that Cox inhibition may have therapeutic potential in epithelial ovarian cancer.

Although previously demonstrated in some other cancer types, until this study, none of the previous studies have analyzed the expression of these markers along with their inter-relations and their correlations with survival in serous ovarian cancer patients who had undergone optimal cytoreduction. The results of our study revealed that E-cadherin expression was significantly associated with better survival. Nonetheless, increased Cox-1 and -2 expressions were in favor of worse survival, while the difference in survival between patients with negative and positive scores did not reach statistical significance.

These results were confirmed with multivariate analyses. When the effects of these 3 markers were evaluated, E-cadherin was determined as the variable which was most related with survival. Negative Cox-2 results were indeed obtained in most patients (78.5%) with positive E-cadherin or most E-cadherin negative patients being Cox-2 positive. Thus, there was an inverse overlapping between E-cadherin and Cox-2. These results support the presence of an inhibitor mechanism between E-cadherin - Cox-2 expression in serous papillary ovarian cancer, as seen in other cancers. Nevertheless, no significant relation could be observed between E-cadherin and Cox-1. This finding can suggest that Cox-1 and E-cadherin are independent factors and are weakly related during carcinogenesis-invasion processes.

A statistical model to determine the contribution of 3 markers individually and in combination to survival prediction (Table 2) was constructed and analyzed by statistician and clinicians. E-cadherin was found to be the most efficient; however addition of Cox-1 and Cox-2 adds little and none, respectively, to this efficiency. The previously mentioned "inverse overlapping" between E-cadherin and Cox-2 may underlie this. On the other hand, efficacy increases with combination E-cadherin and Cox-1, however, addition of Cox-2 to this couple does not improve efficacy further.

Results of our study, especially the inverse correlation between E-cadherin and Cox-2, are in agreement with previous studies investigating the underlying mechanisms of this issue. A predominant mechanism controlling the expression of E-cadherin is transcriptional repression by transcriptional repressors, which include Snail, Slug, SIP1/ZEB1, E12/E47, Twist, and Goosecoid (Jin et al., 2010). There are studies suggesting that E-cadherin expression has been suppressed by over-expression of Snail and it has related with poor survival (Blechschmidt et al., 2008; Yoshida et al., 2009) and tumor progression (Imai et al., 2003; Jin et al., 2005) in ovarian cancer. It was demonstrated that Cox 2 mediated modulation of E cadherin may be through Cox 2 dependent up-regulation of the E cadherin transcriptional repressors, ZEB1 and Snail, which bind to E box elements of the E cadherin promoter (Dohadwala et al., 2006). A recent study showed that Cox-2- dependent prostaglandin E2 in lung cancer cells reduced E-cadherin expression via a ZEB1 and Snail and that inhibition of Cox-2 resulted in rescue of E-cadherin expression (Dohadwala et al., 2006). For tumor cells to dissociate, invade and metastasize, cell-to-cell associations must be disrupted. Cox-2 stimulated the RhoA/Rho kinase pathway which disrupted adherent junction formation by reducing the levels of E-cadherin and α-catenin and increased cell motility (Chang et al., 2006). Moreover, a recent report stated that E-cadherin was inversely correlated with increased VEGF expression which is the strongest mechanism for Cox-2 (Huang et al., 2012).

In this study, the interrelation of these markers with previously defined prognostic factors such as grade, preoperative CA 125, ascites were also investigated and E-cadherin was found to be inversely correlated with ascites volume which was previously demonstrated to be a poor prognostic factor (Chi et al., 2001). We found that ascites volume was larger in E-cadherin negative patients and this finding also supported the absence of E-cadherin expression in poor survival.

The retrospective design and the small number of patients are the limitations of the present study. Patient age may affect survival and a more homogeneous group within a narrower age range would be more appropriate to analyze this probable effect. However, we believe that being the first study evaluating these markers together and our results regarding the prediction of survival will pioneer future studies.

In conclusion, increased expression of E-cadherin was associated with good survival and can be used in survival prediction in serous ovarian cancer patients who had undergone optimal cytoreduction. The inverse correlation between E-cadherin and Cox-2 suggest that these markers are interacting with each other during the carcinogenesis-invasion process. This relation should be clarified with further studies performed on larger patient series. Underlying mechanisms defined above make us think that E-cadherin and Cox-2 may be strongly interrelated in ovarian cancer. On the other hand, the interrelation of Cox-2 and transcription repressors was investigated in other cancers but not yet in ovarian cancer. Such a study will clarify the interrelation and roles of Cox enzymes and adhesion molecules and their action mechanisms in carcinogenesis and invasion. These studies will be leading for new preventive and therapeutic targets.

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