Introduction

Endometrial cancer is the most common gynecologic malignancy in Japan and the western world, where the incidence has dramatically increased over the past decade. The 5-y survival rate for endometrial carcinoma has increased to approximately 80%, which seems to be comparatively higher than those of other malignancies.1 However, patients with deep myometrial invasion, poor differentiation, serous or clear cell histology or extension of disease to other organs or lymph nodes within the pelvic region are at higher risk for disease recurrence.2,3 Endometrial carcinomas can spread via different routes including direct invasion of the myometrium or cervix with, in some cases, subsequent involvement of the uterine serosa and hence potential peritoneal dissemination. Finally, endometrial carcinomas may metastasize to the pelvic and para-aortic lymph nodes, or to distant sites, via lymphatic and hematogeneous routes. The biology of metastasis remains unsolved. The process of tumor metastasis consists of multiple steps, all of which are required to achieve tumor spreading.4,5 Proteins involved in metastasis are natural candidate molecular markers that can be analyzed in archived surgical samples and correlated with tumor recurrence and mortality in retrospective studies. Molecular markers have been studied intensely in endometrial cancer in attempt to predict metastatic potential or clinical outcome,6-10 yet few translate into widespread clinical use. Additional prognostic indicators will contribute to the better detection of patients with a higher risk of relapse or death from disease.

The epithelial-mesenchymal-transition (EMT), meaning changes in cell phenotype from epithelial morphology to mesenchymal morphology, is an important step in the invasion and metastasis of cancer. The EMT has key roles in embryonic development, and the importance in the pathogenesis of cancer and other human diseases is increasingly recognized.11-14 This process of EMT is associated with the progressive redistribution or downregulation of the apical and basolateral epithelial cell-specific tight and adherens junction proteins such as E-cadherin and cytokeratin, and novel expression of mesenchymal molecules such as vimentin and N-cadherin.15,16 One of the key factors that regulates EMT program is the Snail-related zinc-finger...
of transcription factors (Snail and Slug).\textsuperscript{17,18} Snail was first described in Drosophila melanogaster as a regulator of mesoderm formation.\textsuperscript{19} Both Snail and Slug have been suggested to be involved in the acquisition of resistance to apoptosis thereby promoting tumor survival.\textsuperscript{20-22} Therefore, Snail and Slug are thought to be involved in the invasion and metastasis process of cancer cells by promoting an EMT.

Alternations in cellular adhesion molecules such as E-cadherin are important for the development of invasive and metastatic capacity in human cancers.\textsuperscript{23,24} Decreased E-cadherin expression is related to a more infiltrative growth pattern in a variety of cancers,\textsuperscript{25-27} and is an independent prognostic factor of endometrial cancers.\textsuperscript{28,29} The loss of E-cadherin expression is a hallmark of EMT. Other transcriptional factors (Zeb1/def-1, Zeb2/SIP1 and E12/E47) have also been shown to repress the activity of E-cadherin.\textsuperscript{17,30,31} Recent work in hepatocellular carcinoma, oral squamous cell carcinoma and breast cancer\textsuperscript{32-35} suggests that the transcriptional factors of Snail and Slug are important effectors of the process of invasiveness of E-cadherin, a component of adherens junctions.\textsuperscript{36} Moreover, Snail and Slug both play key roles in gynecologic malignancies and also have a prognostic impact.\textsuperscript{37-40} However, no study has so far clarified the prognostic impact of EMT-related protein (E-cadherin, Snails and Slugs) expression in endometrial cancer. Therefore, the

### Table 1. Results of immunohistochemistry

|                      | E-cadherin | Snail (nuclear) | Slug (nuclear) |
|----------------------|------------|----------------|---------------|
|                      | Preserved (%) | Reduced (%) | p value     | Negative (%) | Positive (%) | p value | Negative (%) | Positive (%) | p value |
| Age                  | < 0.0001 | 0.0069 | 0.4760 |               |               |          |               |               |          |
| < 50                 | 57 (83.8) | 11 (16.2) | 64 (94.1) | 4 (5.9) | 67 (98.5) | 1 (1.5) |               |               |          |
| ≥ 50                 | 156 (54.5) | 130 (45.5) | 230 (80.4) | 56 (19.6) | 274 (95.8) | 12 (4.2) |               |               |          |
| BMI                  | 0.0054 | 0.4798 | 0.6230 |               |               |          |               |               |          |
| < 30                 | 185 (57.8) | 135 (42.2) | 264 (82.5) | 56 (17.5) | 307 (95.9) | 13 (4.1) |               |               |          |
| ≥ 30                 | 28 (82.4) | 6 (17.6) | 30 (88.2) | 4 (11.8) | 34 (100.0) | 0 (0.0) |               |               |          |
| Histology            | < 0.0001 | < 0.0001 | < 0.0001 |               |               |          |               |               |          |
| AEH                  | 17 (100.0) | 0 (0.0) | 17 (100.0) | 0 (0.0) | 17 (100.0) | 0 (0.0) |               |               |          |
| Endometrioid G\textsubscript{1} | 128 (80.5) | 31 (19.5) | 145 (91.2) | 14 (8.8) | 159 (100.0) | 0 (0.0) |               |               |          |
| Endometrioid G\textsubscript{2} | 29 (59.2) | 20 (40.8) | 44 (89.8) | 5 (10.2) | 49 (100.0) | 0 (0.0) |               |               |          |
| Endometrioid G\textsubscript{3} | 12 (27.3) | 32 (72.7) | 34 (77.3) | 10 (22.7) | 43 (97.7) | 1 (2.3) |               |               |          |
| Adenoacanthoma        | 15 (83.3) | 3 (16.7) | 17 (94.4) | 1 (5.6) | 18 (100.0) | 0 (0.0) |               |               |          |
| Serous               | 5 (27.8) | 13 (62.2) | 12 (66.7) | 6 (33.3) | 18 (100.0) | 0 (0.0) |               |               |          |
| Clear                | 0 (0.0) | 10 (100.0) | 6 (60.0) | 4 (40.0) | 10 (100.0) | 0 (0.0) |               |               |          |
| Carcinosarcoma       | 1 (4.5) | 21 (95.5) | 8 (36.4) | 14 (63.6) | 12 (54.5) | 10 (45.5) |               |               |          |
| Others               | 6 (35.3) | 11 (64.7) | 11 (64.7) | 6 (35.3) | 15 (88.2) | 2 (11.8) |               |               |          |
| FIGO stage           | < 0.0001 | < 0.0001 | 0.0014 |               |               |          |               |               |          |
| 0                    | 17 (100.0) | 0 (0.0) | 17 (100.0) | 0 (0.0) | 17 (100.0) | 0 (0.0) |               |               |          |
| I                    | 155 (70.5) | 65 (29.5) | 194 (88.2) | 26 (11.8) | 216 (98.2) | 4 (1.8) |               |               |          |
| II                   | 11 (52.4) | 10 (47.6) | 20 (95.2) | 1 (4.8) | 21 (100.0) | 0 (0.0) |               |               |          |
| III                  | 26 (35.1) | 48 (64.9) | 50 (67.6) | 24 (32.4) | 67 (90.5) | 7 (9.5) |               |               |          |
| IV                   | 4 (18.2) | 18 (81.8) | 13 (59.1) | 9 (40.9) | 20 (90.9) | 2 (9.1) |               |               |          |
| Myometrial invasion  | < 0.0001 | 0.0003 | 0.0034 |               |               |          |               |               |          |
| < 50%                | 174 (70.2) | 74 (29.8) | 218 (87.9) | 30 (12.1) | 244 (98.4) | 4 (1.6) |               |               |          |
| ≥ 50%                | 39 (36.8) | 67 (63.2) | 76 (71.7) | 30 (28.3) | 97 (91.5) | 9 (8.5) |               |               |          |
| Peritoneal cytology  | < 0.0001 | < 0.0001 | 0.0058 |               |               |          |               |               |          |
| Positive             | 10 (19.2) | 42 (80.8) | 31 (59.6) | 21 (40.4) | 46 (88.5) | 6 (11.5) |               |               |          |
| Negative             | 203 (67.2) | 99 (32.8) | 263 (87.1) | 39 (12.9) | 295 (97.7) | 7 (2.3) |               |               |          |
| Lymph node metastasis| 0.0002 | 0.0064 | 0.3603 |               |               |          |               |               |          |
| Positive             | 10 (29.4) | 24 (70.6) | 22 (64.7) | 12 (35.3) | 32 (94.1) | 2 (5.9) |               |               |          |
| Negative             | 203 (63.4) | 117 (36.6) | 272 (85.0) | 48 (15.0) | 309 (96.6) | 11 (3.4) |               |               |          |
current study hypothesized that the Snail and Slug expression is related to the E-cadherin suppression in endometrial cancers and investigated the clinical relevance and prognostic impact of the EMT status, based on both a reduced E-cadherin expression and the nuclear Snail or Slug expression in this type of tumor.

**Results**

**E-cadherin expression.** The clinical features of endometrial carcinomas are outlined in Table 1. We investigated the data of patient's age, BMI (body mass index), histology, FIGO stage, myometrial invasion, ascites status, lymph node metastasis and patient’s outcomes. The 354 endometrial tumors included 17 atypical endometrial hyperplasia, 252 endometrioid adenocarcinomas (G1; 159, G2; 49, G3; 44), 18 adenocantheomas, 18 serous adenocarcinomas, 10 clear cell adenocarcinomas, 22 carcinosarcomas and 17 others. Of the 354 investigated patients, 17, 155, 11, 26 and 4 were categorized as stage 0, I, II, III and IV, respectively. Representative examples of immunohistochemically stained sections are shown in Figure 1. Reduced E-cadherin was seen in 39.8% of primary tumors. Reduced E-cadherin was seen in 19.5, 40.8 and 72.7% in G1, G2 and G3 endometrioid adenocarcinoma tumors, respectively. The rates of reduced E-cadherin were significantly higher in the patients with serous, clear cell carcinoma and carcinosarcoma (62.2, 100 and 95.5%, respectively) in comparison to those observed in other histological subtypes. The analysis of FIGO stage revealed the rates to be 0, 29.5, 47.6, 64.9 and 81.8% in stage 0, I, II, III and IV, respectively. The rate of reduced E-cadherin in advanced cancer (stage III and IV) was significantly higher than that of early cancer (stage 0, I and II). Reduced E-cadherin expression was observed in 29.8% of the cases with less than 50% myometrial invasion, on the other hand, 63.2% in the cases more than a half of myometrial invasion. A reduced E-cadherin expression was observed in 80.8% of the patients with positive peritoneal cytology, in comparison to 32.8% in the patients with negative peritoneal cytology (p < 0.0001). In addition, the rates of the reduced E-cadherin expression were significantly higher in the patients with positive lymph node metastasis than that with negative metastasis (p = 0.0002).

**Snail expression.** Snail expression was observed mainly in the cytoplasm; therefore, any cell with nuclear Snail staining was identified as positive. The cytoplasmic staining was unexpected, because Snail was originally identified as a transcription factor. Nuclear expression of Snail was detected in 16.9% of primary tumors. The rates of Snail expression were significantly higher in G3 endometrioid tumors than that of G1 and G2 tumors. Moreover, the rates of nuclear expression of Snail were significantly higher in the patients of serous, clear cell carcinoma and carcinosarcoma (33.3, 40 and 63.6%, respectively) than that in other histological subtype. The analysis of FIGO stage revealed that the rates of nuclear expression of Snail were 0, 11.8, 4.8, 32.4 and 40.9% in stage 0, I, II, III and IV, respectively. The rate of reduced E-cadherin expression was significantly higher in advanced cancer (stage III and IV) than that of early cancer (stage 0, I and II). Snail positive cells were observed in 12.1% of cases with less than 50% myometrial invasion. On the other hand, positive cells were observed in 28.3% of the cases with more than 50% myometrial invasion. A reduced E-cadherin expression was observed in 80.8% of the patients with positive peritoneal cytology, in comparison to 12.9% in the patients with negative peritoneal cytology. In addition, the rates were 35.3 and 15.0% in lymph node-positive and -negative patients, respectively. Positive Snail immunoreactivity was also associated with all variables except BMI.

**Slug expression.** Slug expression was identified as positive if nuclear staining was observed, as described with Snail expression. The nuclear expression of Slug was seen in only 3.7% of primary tumors. Interestingly, the nuclear expression of Slug was frequently recognized in carcinosarcomas. The analysis of FIGO
associated with a reduced expression of E-cadherin in this study. These findings were particularly noticeable at the invasive front of tumor (Fig. 1), thus EMT status was represented by both reduced E-cadherin expression and nuclear Snail expression (Fig. S1). The results of immunohistochemistry were compared with the patient survival. Overall survival and progression-free survival were stratified according to the EMT status with the Kaplan-Meier method using a log-rank test (Fig. 2). EMT status was significantly associated with patient survival (p < 0.05). A multivariate analysis using the Cox proportional hazards models was conducted to assess the predictive value of the tumor EMT status (Table 3). The analysis included the following prognostic variables: FIGO stage, histological types (endometrioid/non endometrioid), myometrial invasion (< 50%/ > 50%), peritoneal cytology (positive/negative), lymph node metastasis (positive/negative). EMT-positive status (95% CI, 0.249–0.791; p = 0.0059) along with the FIGO stage (95% CI, 1.180–6.964; p = 0.0201), the initial histological type (endometrioid/non endometrioid; 95% CI, 1.534–4.936; p = 0.0007), myometrial invasion (< 50%/ > 50%; 95% CI, 1.481–5.704; p = 0.0019) and peritoneal cytology (95% CI, 0.226–0.906; p = 0.0252) were found to be significant predictors of progression-free survival (Table 3). EMT-positive status (95% CI, 0.197–0.678; p = 0.0014) along with the initial histological type (endometrioid/non endometrioid; 95% CI, 1.564–5.485; p = 0.0008), myometrial invasion (< 50%/ > 50%; 95% CI, 1.773–7.639; p = 0.0005) and peritoneal cytology (95% CI, 0.170–0.783; p = 0.0097) were identified to be significant predictors of overall survival (Table 3). The results of the multivariate survival analyses are also summarized in Table 3.

Discussion

The current study revealed that the overexpression of Snail and Slug was closely associated with the reduced expression of E-cadherin in uterine endometrial cancer, and these findings were particularly noticeable at the invasive front of the tumor. Malignant epithelial tumors can invade surrounding tissues through a variety of mechanisms.41 EMT is considered to be an important means of tumor invasion and metastasis in many common cancers. The current study is the first report to demonstrate that the EMT status, as represented by both reduced E-cadherin expression and nuclear Snail expression, was identified to be an independent predictive factor of patient survival in endometrial cancer. Although we also evaluated the vimentin status, which was one of the mesenchymal markers in this tissue microarray sample to confirm the mesenchymal status, the rate of vimentin expression showed no substantial differences associated with the

| Variables | Primary | Metastases | p value |
|-----------|---------|------------|---------|
| E-cadherin | n = 30 (%) | n = 30 (%) | 0.11 |
| reduced | 20 (66.7) | 14 (46.6) | |
| preserved | 10 (33.3) | 16 (53.4) | |
| Snail | 0.78 |
| positive | 10 (33.3) | 11 (36.7) | |
| negative | 20 (66.7) | 19 (63.3) | |
| Slug | 0.60 |
| positive | 2 (6.7) | 2 (6.7) | |
| negative | 28 (93.3) | 28 (93.3) | |
FIGO stage or in the histological subtypes, the rate of vimentin expression was not associated with myometrial invasion, peritoneal cytology and lymph node metastasis status (Table S1 and Fig. S2). These results were almost identical to those described in a previous report. Therefore, we believe that the vimentin expression should be excluded as a marker of the EMT status in the current study. The transcription factor Snail is one of the repressors involved in E-cadherin downregulation. Snail is thought to be an important regulator of invasiveness during tumor progression. The current study found a statistically significant inverse relationship between the Snail and E-cadherin expression in endometrial cancer. Specifically, the overexpression of Snail was closely associated with either the absence or a reduced expression of E-cadherin at the invasive front of tumors. Moreover, we showed the first report that EMT status, which was represented by both reduced E-cadherin expression and nuclear Snail expression, was associated with a significantly increased risk of death. An association was observed between the Snail expression and lymph node metastasis. However, there was no correlation between the Snail expression in primary tumors and their corresponding metastases, thus suggesting that the immunohistochemistry cannot directly demonstrate the status of invasive malignant cells. Further examination in vitro is therefore required to clarify whether Snail regulates the E-cadherin reduction, and Snail and E-cadherin regulate the invasiveness and metastasis of cancer cells in endometrial cancer.

The carcinosarcoma patients in the current series showed high expression rates of not only Snail but also Slug. Slug is overexpressed in numerous cancers, including ovarian cancer, breast cancer, prostate cancer, esophageal cancer, gastric cancer, colorectal cancer, pancreatic cancer, lung cancer, leukemia, malignant mesothelioma, cholangiocarcinoma, hepatocellular carcinoma and glioma. An elevated expression of Slug is also associated with reduced E-cadherin expression, high histologic grade, lymph node metastasis, postoperative relapse and a shorter patient survival in a variety of cancers. In other words, Slug overexpression could contribute to downregulate the expression of E-cadherin and induce EMT in epithelial cells. However, Snail and Slug may differ in their respective target genes. Forced overexpression of each of these transcription factors induces EMT in cancer cell lines. Slug is also more relevant for generating breast cancer cells with cancer cell phenotype than Snail. Slug overexpression was rare in endometrial cancer in the current study, but was selectively expressed in carcinosarcoma patients, and 10 of 13 positive cases were carcinosarcoma patients. Slug might thus be strongly involved in E-cadherin downregulation in carcinosarcoma, leading to the tumor cells acquiring the ability of metastasis and might be a more important regulator of the EMT in carcinosarcoma than that in endometrioid adenocarcinoma. These findings suggest that Slug might be a crucial factor that regulates the EMT program. However, the current study showed the immunoreactivity status of the EMT program in endometrial cancer. Further examination in vitro is necessary to clarify whether Slug regulates the reduction of E-cadherin, and whether Slug and E-cadherin regulate the cancer cells invasive and metastatic behavior in uterine carcinosarcoma.

In conclusion, the current study demonstrated that EMT status, which was represented by both reduced E-cadherin expression and nuclear Snail expression, was an independent predictor in endometrial cancer. Moreover, Slug might be the crucial factor that regulates EMT program in uterine carcinosarcoma. These results indicate that E-cadherin and Snail or Slug may therefore be potentially useful molecular targets in endometrial cancer.

Material and Methods

Tissue samples. Tissue samples were obtained from 354 Japanese patients who underwent surgical resection for primary endometrial carcinomas at Osaka Medical College. The Institutional Review Board approved this study and informed consent was obtained from all patients. These specimens were fixed in 10% formalin and embedded in paraffin. Serial sections cut out from paraffin-embedded blocks were used for routine histopathology. A 4 μm section was cut from a tissue microarray block and immunohistochemically analyzed for the expression of E-cadherin, Snail and Slug. The specimens of the primary tumor as well as the corresponding lymph node metastases from 30 cases were also analyzed.
Immunohistochemistry. Tumor samples were formalin-fixed and embedded in paraffin. Deparaffinized and rehydrated sections (4 μm) were autoclaved in 0.01 mol/l citrate buffer pH 6.0 for 15 min at 121°C for antigen retrieval. Endogenous peroxidase activity was blocked with 0.3% solution hydrogen peroxide in methanol for 30 min. Tumor sections were incubated at 4°C for 12 h with the E-cadherin-specific antibodies E-cadherin (24E10; 1:50 dilution; Cell signaling Technology), Snail antibody (N-term D24; 1:100 dilution; ABGENT) and Slug antibody (C19G7 1:50 dilution; Cell signaling Technology). The sections were washed with 1X phosphate-buffered saline (PBS) and incubated with Histofine simple stain MAX PO (multi; Nichirei) for 30 min at room temperature. Finally, the sections were washed with 1X PBS, signals and then were visualized by incubation with H₂O₂/diaminobenzidine substrate solution for 5 min. The sections were counterstained with hematoxylin prior to dehydration and mounting. Evaluation of the immunohistochemical data was performed by two independent pathologists who were blinded to the clinicopathological data. The expression of e-cadherin, Snail and Slug was assessed using a semiquantitative system that was defined as described by Blechschmidt et al.37 Briefly, E-cadherin expression was scored as: 0 (no stain), 1+ (low intensity immunoreactivity in more than 10% of tumor cells), 2+ (medium intensity immunoreactivity of more than 10% of tumor cells), 3+ (high intensity immunoreactivity of more than 10% of tumor cells). These data were summarized into two groups; preserved E-cadherin (3+) and reduced E-cadherin (0, 1+, 2+). The Snail and Slug expressions were evaluated as positive only when nuclear staining was detectable: 0 (no stain), 1+ (immunoreactivity of more than 1% of tumor cells), 2+ (immunoreactivity of more than 2–5% of tumor cells), 3+ (immunoreactivity of more than 5% of tumor cells), then divided into two groups, negative (0), and positive (1+, 2+, 3+). Scoring was performed three times per slide for three distinct fields, and the three scores were averaged.

Statistical analysis. Statistical analyses in this study were performed with the StatView statistical software package (SAS Institute). Fisher’s exact probability test was used for evaluating correlations between immunohistochemical and clinical data. The end points investigated were the progression-free and overall survival (PFS and OS). The progression-free survival was defined as the time from the first day of treatment until either death from any cause or disease progression. Overall survival was defined as time from the first day of treatment to death from any cause. Univariate and multivariate analyses of the progression-free survival and overall survival were determined with the Kaplan-Meier method using a log-rank test and the Cox proportional hazards model, respectively. Differences with p values of less than 0.05 were considered to be statistically significant.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Acknowledgments
This work was supported by a grant-in-aid for Scientific Research on Priority Areas, number 22591869 (to Y.T.) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

Supplemental Materials
Supplemental materials may be found here: http://www.landesbioscience.com/journals/cbt/article/22625/
21. Pérez-Louda J, Sánchez-Martín M, Pérez-Cano M, Pérez-Mencera PA, Sánchez-García I. The radiosensitization biomolecular function of the SCF/kit signaling pathway is mediated by the zinc-finger transcription factorSlug. Oncogene 2003; 22:4205-11; PMID:12833143; http://dx.doi.org/10.1038/sj.onc.1206467.

22. Vega S, Morales AV, Ocata OH, Valdés F, Fabregat I, Nieto MA. Snail blocks the cell cycle and confers resistance to cell death. Genes Dev 2004; 18:1131-43; PMID:15155580; http://dx.doi.org/10.1101/gad.294104.

23. Takeichi M. Cadherins in cancer: implications for invasion and metastasis. Curr Opin Cell Biol 1993; 5:806-11; PMID:8240824; http://dx.doi.org/10.1016/0955-2078(93)90029-F.

24. Wijnhoven BP, Dinjens WN, Pignataro M. E-cadherin-catenin cell-cell adhesion complex and human cancer. Br J Surg 2000; 87:1005-10; PMID:10931041; http://dx.doi.org/10.1046/j.1365-2168.2000.01513.x.

25. Sakuragi N, Nishiya M, Ikeda K, Ohkouch T, Furth EE, Hareyama H, et al. Decreased E-cadherin expression is associated with tumour dedifferentiation and deep myometrial invasion. Gynecol Oncol 1994; 53:183-9; PMID:8188077; http://dx.doi.org/10.1006/gyno.1994.1113.

26. Cheng L, Nagabushan M, Prewoll TP, Amini SB, Prewoll TG. Expression of E-cadherin in primary and metastatic prostate cancer. Am J Pathol 1996; 148:1375-80; PMID:8623999.

27. Brendes RM, Veve R, Gabrielson E, Hirsch FR, Baron A, Bemis L, et al. High-throughput tissue microarray analysis used to evaluate biology and prognostic significance of the E-cadherin pathway in non-small-cell lung cancer. J Clin Oncol 2002; 20:2477-28; PMID:12101119; http://dx.doi.org/10.1200/JCO.2002.08.159.

28. Graff JR, Herman JG, Lapidus RG, Chopra H, Xu R, Jarrett DE, et al. E-cadherin expression is silenced by DNA hypermethylation in human breast and prostate carcinomas. Cancer Res 1995; 55:1593-9; PMID:7585573.

29. Yoshura K, Kanai Y, Ochiai A, Shimoyama Y, Sugimura T, Hirohashi S. Silencing of the E-cadherin invasion-suppressor gene by CpG methylation in human breast and prostate carcinomas. Cancer Res 1995; 55:1593-9; PMID:7585573.

30. Grooteclaes ML, Frisch SM. Evidence for a function of CBP in epithelial gene regulation and anoikis. Oncogene 2000; 19:3823-8; PMID:10949939; http://dx.doi.org/10.1038/sj.onc.1206546.

31. Comijn J, Bers G, Vermassen P, Verschueren K, van Grunsven L, Bruynel E, et al. The two-handed E box binding zinc finger protein SIP1 downregulates E-cadherin and induces invasion. Mol Cell 2001; 7:1267-78; PMID:11430829; http://dx.doi.org/10.1016/s1097-2765(01)00260-x.

32. Blanco MJ, Moreno-Bueno G, Sarrío D, Locascio A, Cano A, Palacios J, et al. Correlation of Snail expression with histological grade and lymph node status in breast carcinomas. Oncogene 2002; 21:3241-6; PMID:12082640; http://dx.doi.org/10.1038/sj.onc.1205416.

33. Grille SJ, Belloca A, Usson J, Klein-Szanto AJ, van Roy F, Lee-Kwon W, et al. The protein kinase Akt induces epithelial mesenchymal transition and promotes enhanced mobility and invasiveness of squamous cell carcinoma lines. Cancer Res 2003; 63:2172-8; PMID:12727836.

34. Sugimachi K, Tanaka S, Kameyama T, Taguchi K, Aishima S, Shimada M, et al. Transcriptional repression snail and progression of human hepatocellular carcinoma. Clin Cancer Res 2003; 9:2657-64; PMID:1285644.

35. Bolós V, Peinado H, Carreño F, Hoeftler H, Becker KE. Role of the epithelial-mesenchymal transition regulator Slug in primary human cancers. Front Biosci 2009; 14:3035-50; PMID:19273255; http://dx.doi.org/10.2741/3433.

36. Batlle E, Sancho E, Francic G, Dominguez D, Moníbar M, Baudida J, et al. The transcription factor snail is a repressor of E-cadherin gene expression in epithelial tumour cells. Nat Cell Biol 2000; 2:76-83; PMID:10655580; http://dx.doi.org/10.1038/35000034.

37. Bähler E, Sancho E, Francic G, Dominguez D, Moníbar M, Baudida J, et al. The transcription factor snail is a repressor of E-cadherin gene expression in epithelial tumour cells. Nat Cell Biol 2000; 2:76-83; PMID:10655580; http://dx.doi.org/10.1038/35000034.

38. Belechschmidt K, Sassen S, Schmalfeldt B, Schuster T, Höfler H, Becker KE. The E-cadherin repressor Snail is associated with lower overall survival of ovarian cancer patients. Br J Cancer 2008; 99:489-95; PMID:18026186; http://dx.doi.org/10.1038/sj.bjc.6604115.

39. Tukkanen H, Soini Y, Kosma VM, Austrila M, Sironen R, Hamalainen K, et al. Nuclear expression of Snail in borderline and malignant epithelial ovarian tumours is associated with tumour progression. BMC Cancer 2009; 9:289; PMID:19095091; http://dx.doi.org/10.1186/1471-2407-9-289.

40. Kurrey NK, A, Bapat SA. Snail and Slug are major determinants of ovarian cancer invasion aggressiveness at the transcription level. Gynecol Oncol 2005; 97:155-65; PMID:15790452; http://dx.doi.org/10.1016/j.ygyno.2004.12.043.

41. Ellouël S, Eltrand MB, Nesland JM, Tripol CG, Kvalheim G, Goldberg I, et al. Snail, Slug, and Smad-interacting protein 1 as novel parameters of disease aggressiveness in metatstatic ovarian and breast carcinoma. Cancer 2005; 103:1631-43; PMID:15742334; http://dx.doi.org/10.1002/cncr.20946.

42. Yilmaz M, Christofori G, Lehembre F. Distinct mechanisms of tumor invasion and metastasis. Trends Mol Med 2007; 13:535-41; PMID:17798156; http://dx.doi.org/10.1016/j.molmed.2007.10.004.

43. Coppola D, Fu L, Nicosia SV, Koundis S, Jones M. Prognostic significance of p53, bcl-2, vimentin, and S100 protein-positive Langerhans cells in endometrial carcinoma. Hum Pathol 1998; 29:455-62; PMID:9595268; http://dx.doi.org/10.1006/hump.1998.5060.

44. Cano A, Pérez-Moreno MA, Rodrigo I, Locascio A, Blanco MJ, del Barrio MG, et al. The transcription factor snail controls epithelial-mesenchymal transitions by repressing E-cadherin expression. Nat Cell Biol 2000; 2:76-83; PMID:10655586; http://dx.doi.org/10.1038/35000025.

45. Bolós V, Peinado H, Pérez-Moreno MA, Fraga MF. Snail, Slug, and E47 repressors. J Cell Sci 2003; 116:499-511; PMID:12508111; http://dx.doi.org/10.1242/jcs.00224.

46. Kurrey NK, Jalgaonkar SP, Joglekar AV, Ghanate AD, Chaskar PD, Doiphode RY, et al. Snail and slug mediate radiosensitization and chemoresistance by antagonizing p53-mediated apoptosis and acquiring a stem-like phenotype in ovarian cancer cells. Stem Cells 2009; 27:2059-66; PMID:19544473; http://dx.doi.org/10.1002/stem.154.

47. Bhat-Nakshatri P, Appaiah H, Ballas C, Pick-Franke P, Goulet R Jr, Badve S, et al. SLUG/SNAI2 and tumor necrosis factor alpha generate breast cells with CD44+/CD24- phenotype. BMC Cancer 2010; 10:411; PMID:20601079; http://dx.doi.org/10.1186/1471-2407-10-411.