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Decreased expression of the adhesion molecule desmoglein-2 is associated with diffuse-type gastric carcinoma

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ABSTRACT

Desmoglein-2 (Dsg2) is one of the components of the cell–cell adherence junction. We previously reported that loss of heterozygosity at chromosome 18q12, on which the *Dsg2* gene exists, is frequently found in diffuse-type gastric cancers. This study investigated the relationship between Dsg2 expression and diffuse-type gastric cancers. A total of 112 primary tumours resected from patients with gastric cancer were stained with a monoclonal antibody against Dsg2 and examined for correlations between the expression of Dsg2 and various clinicopathological factors, including loss of heterozygosity on chromosome 18q and prognosis. Dsg2 is immunolocalised at cell–cell boundaries in normal gastric mucosa. Loss of Dsg2 expression was observed in 33 of 112 gastric tumours. There was a statistically significant correlation between a decrease in Dsg2 staining and loss of tumour differentiation ($P < 0.001$), tumour macroscopic feature ($P < 0.001$) and peritoneal dissemination ($P = 0.023$), and Dsg2-negative staining was correlated significantly with loss of heterozygosity on chromosome 18q12 ($P = 0.001$). The prognosis of patients with Dsg2-negative tumours was significantly worse than that of those with Dsg2-positive tumours (log rank, $P < 0.01$), while multivariate analysis revealed that Dsg2 was not an independent prognostic factor. These findings suggest that decreased expression of Dsg2 is associated with diffuse-type gastric cancers and poor prognosis in gastric carcinoma.

1. Introduction

Epithelial cell–cell adhesion is important in tumour development. Two adhering-type junctions, the desmosome and adherens junctions, are responsible for strong cell–cell adhesion. Each of these junctions consists of a transmembrane cadherin and a complex cytoplasmic plaque that serve to link cadherin to actin microfilaments or the intermediate filament cytoskeleton.[1] Intercellular junctions known as desmosomes are multimolecular membrane domains that provide intercellular adhesion and membrane anchors for the intermediate filament cytoskeleton.[2] Desmosomes contain the desmosomal cadherins, desmogleins (Dsgs) and desmocollins that are linked to the intermediate filament cytoskeleton through interactions with plakoglobin and desmoplakin.[1,3,4] The adherens junction is composed of a classic cadherin (e.g. E-, P- or N-cadherin) linked to β-catenin or plakoglobin.[5,6] Thus, plakoglobin is found in both adherens junctions and desmosomes, while β-catenin is restricted to the adherens junction.[1,7,8] Alpha-catenin links the cadherin/catenin complex to the actin cytoskeleton through interactions with β-actinin, vinculin, ZO-1 and actin filaments.[9,10] Lost or reduced plakoglobin expression has been observed in tumour tissues and metastatic lesions, and has been linked to poor prognosis in a variety of tumours.[11]

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Dsgs are transmembrane glycoproteins of the desmosome, a cell–cell adhesive structure prominent in epithelial tissues,[12] which have been reported to be associated with tumour development.[2] cDNA and protein studies have revealed that there are subfamilies of Dsgs (types 1, 2 and 3) and desmocollins (types 1, 2 and 3).[13] Type 2 Dsg (Dsg2), but not type 1 or 3, is expressed in stomach epithelia.[14] We previously reported that loss of heterozygosity (LOH) on chromosome 18q12 in diffuse-type gastric cancer is significantly higher than in intestinal-type gastric cancer, and we suggested that *Dsg2*, which exists at 18q12, might be a candidate tumour suppressor locus in diffuse-type gastric cancers.[15]

Gastric cancers have been classified into two histological types: intestinal-type and diffuse-type. Diffuse-type gastric cancers show decreased cell–cell adhesion, which is associated with metastatic potential. These histological features indicate that a decrease in adhesive junctions may be involved in the emergence of diffuse-type gastric cancers. A decrease in E-cadherin has been reported to be one cause of the decrease in adhesive junctions, but not all diffuse-type gastric cancers show such a decrease.[16,17] Although Dsg2 may play an important role in the carcinogenesis of gastric cancer, to the best of our knowledge, there is only one report in the literature on Dsg2 and gastric cancer.[18] In the present study, we investigated the relationship between Dsg2 expression and clinicopathological characteristics in gastric cancer.

2. Materials and methods

2.1. Clinical materials

A total of 112 patients who had undergone resection of a primary gastric tumour at our institute between 1988 and 1996, and who were histologically confirmed to have sporadic advanced gastric cancer were enrolled in the present study. Advanced cancer was defined as cancer invasion into the muscularis propria or serosa. Tumour specimens were fixed in 10% formaldehyde solution *v/v* and embedded in paraffin. Sections 4 μm thick were cut and mounted on glass slides. The pathological diagnoses and classifications were made according to the Japanese Classification of Gastric Carcinoma provided by the Japanese Gastric Cancer Association (JGCA).[19] The median follow-up time for all 112 patients was 33.4 months (range 0.7–107 months). The median follow-up time for the patients who died of the disease was 20.7 months ($n = 58$) compared with 46.9 months for surviving patients ($n = 54$). Twenty-seven patients were lost from more than 60 months of follow-up. The survival curve shows Kaplan–Meier overall survival curves in relation to Dsg2 expression levels in gastric carcinomas. The survival curve was calculated from the date of surgery.

2.2. Antibodies and reagents

A mouse monoclonal antibody that recognises Dsg2 was purchased from Progen Biotechnik GmbH (clone 10G11, catalogue number 61059; Heidelberg, Germany), and a mouse monoclonal antibody that recognises *E*-cadherin was purchased from Santa Cruz Biotechnology, Inc. (clone *G*-10, catalogue number sc8426; Santa Cruz, CA, United States of America (USA)). Normal rabbit serum, normal mouse immunoglobulin *G*, biotinylated rabbit anti-mouse immunoglobulin *G*, streptavidin-peroxidase reagent and diaminobenzidine were purchased from Nichirei Corporation (Tokyo, Japan).

2.3. Immunohistochemical techniques

The methods for the immunohistochemical determination of Dsg2 and *E*-cadherin are described in detail in the manufacturers' instructions. Briefly, the slides were deparaffinised in xylene and hydrated in decreasing concentrations of ethyl alcohol. The tissues were heated for 20 min at 105 °C and at 0.4 kg/cm^2 by autoclave in Target Retrieval Solution (Dako Co., Carpinteria, CA, USA). The sections were then de-waxed and incubated with 3% hydrogen peroxide *v/v* in methanol for 15 min to block endogenous peroxidase activity. Next, the sections were washed in phosphate buffered saline (PBS) and incubated in 10% normal rabbit serum *v/v* for 10 min to reduce non-specific antibody binding. The specimens were incubated with Dsg2 antibody (2.5 μg/ml) or *E*-cadherin antibodies (4 μg/ml) for 1 h at room temperature, or overnight at 4 °C, followed by three washes with PBS. Sections were incubated with biotinylated rabbit anti-mouse immunoglobulin *G* for 30 min, followed by three washes with PBS. Slides were treated with streptavidin-peroxidase reagent for 15 min and washed with PBS three times. Finally, the slides were incubated in PBS diaminobenzidine and 1% hydrogen peroxide *v/v* for 20 s, counterstained with Mayer's haematoxylin and mounted.

2.4. Immunohistochemical determination of Dsg2 and E-cadherin

The tumour specimens showed various staining patterns against anti-Dsg-2 antibody and anti-*E*-cadherin antibody. The degree of monoclonal antibody reactivity in individual tissue sections was considered positive if unequivocal staining of the membrane, that is, staining as strong as that seen in the normal epithelium, was seen in more than 20% of tumour cells. The slides were interpreted by two investigators without knowledge of the corresponding clinicopathological data.

2.5. Analysis of loss of heterozygosity at the 18q locus

Analysis of 18q LOH was performed as previously described.[15] Tumoural or corresponding normal DNA was extracted from sections (10 μm thick) cut from the 10% buffered v/v formalin-fixed paraffin-embedded tissue. The average number of microdissected cells was 3000. One section was stained with haematoxylin, and this reference slide was used under a dissection microscope to select areas for microdissection using a sterile scalpel blade. Genomic DNA was isolated from the paraffin-embedded microdomains and removed from the slides, then extracted using Proteinase K (Gibco, Gaithersburg, MD, USA). Polymerase chain reaction (PCR) was performed using three primer sets for microsatellite loci *D18S474*, *D18S34* and *D18S56* on 18q; *D18S34* is located at 18q12, where Dsg-2 genes exist. *D18S474* and *D18S56* are located on the telomere and centromere sides of *D18S34*, respectively. The following primers were used: *D18S474*, sense, 5′-TGGGGTGTTTACCAG-

CATC-3′ and antisense, 5′-TGGCTTTCAATGTCAGAAGG-3′; *D18S34*, sense, 5′-CAGAAAATTCTCTCTGGCTA-3′ and antisense, 5′-CTCATGTTCCTGGCAAGAAT-3′; *D18S56*, sense, 5′-TATCTCCTGAAGGACCTGCC-3′ and antisense, 5′-CTGCCAGTTGTATAAACGCC-3′. In brief, each 4-μl reaction mixture containing 2 μl of DNA template, 10 mM Tris-HCl (pH 8.3), 50 mM KCl, 1.5 μM $MgCl_2$, 0.025 μM of sense primer labelled with γ^{32}P ATP and unlabelled antisense primer, 200 μM dNTPs, and 0.5 U of AmpliTaq Gold (Applied Biosystems, Foster City, CA, USA) was amplified for 38 cycles under the following regimen: denaturation at 95 °C for 40 s, annealing at 56 °C for 40 s, and extension at 72 °C for 40 s. The PCR products were denatured and electrophoresed in 6% polyacrylamide w/v 8 M urea gels. The gel was dried on a filter paper and autoradiographed overnight at room temperature on X-ray film. Densitometry was used to analyse allele intensities. The gel image was captured with a GS-690 Imaging Densitometer (Bio-Rad Laboratories, Hercules, CA, USA), digitised at 300 dpi, and analysed using Multi-Analyst Ver. 1 (Bio-Rad). A tumour was defined as exhibiting LOH when its signal was absent or showed more than 50% reduction with respect to that observed on the normal counterpart. 18q LOH was identified when at least 2 of 3 markers showed LOH in each case. In the present study, LOH analysis was performed on 90 of the 112 gastric cancer cases previously reported by Nishioka and colleagues;[15] LOH at *D18S4744*, *D18S34* and *D18S56* was not informative in 90 cases in this previous report.

2.6. *Statistical analysis*

We used the χ^2 test, Fisher's exact test or Mann–Whitney *U* test to determine the significance of the differences between the covariates. Survival durations were calculated using the Kaplan–Meier method and were analysed by the log-rank test to compare the cumulative survival durations in the patient groups. The Cox proportional hazards model was used to compute univariate and multivariate hazards ratios for the study parameters. For all tests, a *P*-value of less than 0.05 was defined as statistically significant. The SPSS software program (SPSS Japan, Tokyo, Japan) was used for the analyses.

3. Results

3.1. *Desmoglein-2 and E-cadherin expression in gastric cancer*

Dsg2 and E-cadherin were primarily immunolocalised at cell–cell boundaries, and to some extent in the cytoplasm in normal gastric mucosa. The expression of both Dsg2 and E-cadherin was observed at cell–cell boundaries in an intestinal-type carcinoma. Differential expression levels between Dsg2 and E-cadherin were found in cancer cells. Decreased expression of Dsg2 was observed in some lesions with normal expression of E-cadherin, and decreased expression of E-cadherin was also found in some lesions with normal expression

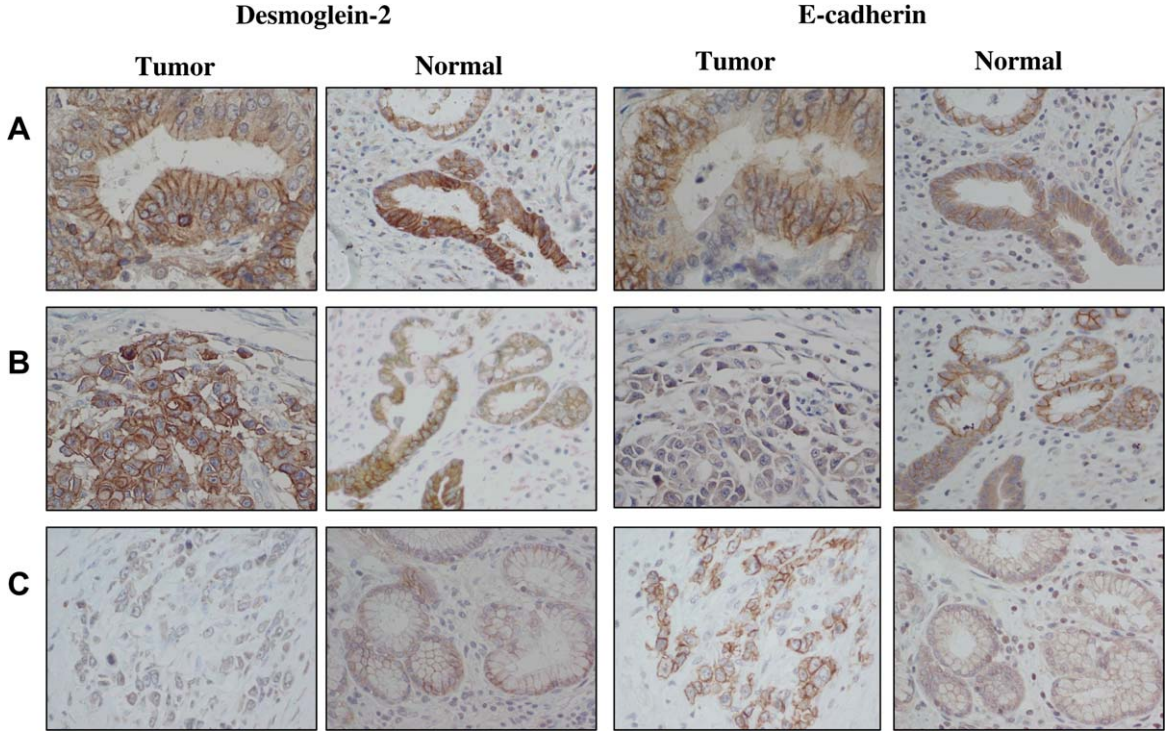

Fig. 1 – Desmoglein-2 and E-cadherin expression. (A) The expression of both Dsg2 and E-cadherin was observed at cell–cell boundaries in an intestinal-type carcinoma. Lesions with Dsg2 expression were somewhat different from those with E-cadherin expression. (B) Abnormal expression of E-cadherin was observed in a diffuse-type cancer with normal expression of Dsg2. (C) Decreased expression of Dsg2 was observed in a diffuse-type cancer with normal expression of E-cadherin. Normal gastric mucosa at cell–cell boundaries was immunoreactive with anti-Dsg-2 antibody and anti-E-cadherin antibody. Original magnification, 200×.

of Dsg2 (Fig. 1(A)). Decreased expression of E-cadherin was also observed in a diffuse-type cancer with normal expression of Dsg2 (Fig. 1(B)). Decreased expression of Dsg2 was observed in a diffuse-type cancer with normal expression of E-cadherin (Fig. 1(C)).

3.2. *Correlation between clinicopathological factors and desmoglein-2 and/or E-cadherin expression*

Dsg2 expression was negative in 33 (29%) of 112 gastric tumours. Table 1 shows the relationship between Dsg2 and clinicopathological features. Forty-one percent (31/75) of diffuse-type cancers showed Dsg2-negative staining, while only 5% (2/37) of intestinal-type cancers showed negative staining. Dsg2 expression had a significantly negative correlation with tumour differentiation ($P < 0.001$), tumour macroscopic features ($P < 0.001$), T stage as depth of tumour invasion ($P = 0.012$), and peritoneal dissemination ($P = 0.023$). In contrast, a positive correlation with venous invasion was found ($P = 0.042$). There was no statistically significant association between Dsg2 expression and patient gender, age, hepatic metastasis or lymph node disease.

E-cadherin expression was negative in 47 (42%) of 112 gastric tumours. Fifty-five percent (41/75) of diffuse-type cancers

Table 1 – Correlation between desmoglein-2/E-cadherin staining and clinicopathological features

Clinicopathological features	Desmoglein-2 expression		P-value	E-cadherin expression		P-value	Desmoglein-2/E-cadherin expression		P-value
	Negative ($n = 33$)	Positive ($n = 79$)		Negative ($n = 47$)	Positive ($n = 65$)		Either negative ($n = 64$)	Both positive ($n = 48$)	
Gender (male/female)	21/12	57/22	NS	28/19	50/15	NS	39/25	39/9	NS
Age (year, mean ± SD)	60 ± 12	62 ± 10	NS	63 ± 10	61 ± 12	NS	63 ± 11	60 ± 10	NS
Morphologic feature[a]									
Type 1	1 (8%)	11	<0.001	2 (17%)	10	<0.035	3 (25%)	9	<0.001
Type 2	3 (11%)	25		9 (32%)	19		12 (43%)	16	
Type 3	3 (14%)	19		8 (36%)	14		10 (45%)	12	
Type 4	26(52%)	24		28 (56%)	22		39 (78%)	11	
Differentiation									
Diffuse type	31 (41%)	44	<0.001[c]	41 (55%)	34	<0.001[d]	56 (75%)	19	<0.001[d]
Intestinal type	2 (5%)	35		6 (16%)	31		8 (22%)	29	
T stage									
T2	2 (8%)	23	0.012	7 (28%)	18	0.396	9 (36%)	16	0.074
T3	28 (35%)	51		36 (46%)	43		49 (62%)	30	
T4	3 (38%)	5		4 (50%)	4		6 (75%)	2	
Peritoneal metastasis									
Positive	13 (46%)	15	0.023[d]	14 (48%)	15	0.28[d]	22 (76%)	7	0.015[d]
Negative	20 (24%)	64		33 (40%)	50		42 (51%)	41	
Hepatic metastasis									
Positive	2 (29%)	5	0.96[c]	3 (43%)	4	0.63[c]	4 (57%)	3	0.66[c]
Negative	31 (30%)	74		44 (42%)	61		60 (57%)	45	
Venous invasion									
Positive	11 (20%)	43	0.042[d]	20 (37%)	34	0.20[d]	28 (52%)	26	0.184[d]
Negative	22 (38%)	36		27 (47%)	31		36 (62%)	22	
Lymph node metastasis									
Positive	25 (30%)	59	0.9[d]	37 (44%)	47	0.292[d]	50 (60%)	34	0.253[d]
Negative	8 (29%)	20		10 (36%)	18		14 (50%)	14	
Lymphatic invasion									
Positive	27 (32%)	57	0.28[d]	33 (39%)	51	0.219[d]	48 (57%)	36	0.585[d]
Negative	6 (21%)	22		14 (50%)	14		16 (57%)	12	
Loss of heterozygosity on 18q[b]									
LOH-positive	17 (71%)	7	0.001[d]	9 (38%)	15	0.438[d]	20 (83%)	4	0.002[c]
LOH-negative	11 (20%)	45		23 (41%)	33		26 (46%)	30	

a Classification according to the general rules for gastric cancer study of the Japanese Research Society for Gastric Cancer. Type 1 is defined as a polypoid tumour, sharply demarcated from the surrounding mucosa and usually attached on a wide base. Type 2 is defined as polypoid tumour with ulceration and with sharply demarcated margins. Type 3 is defined as ulcerated carcinoma with cancer infiltration into the surrounding wall. Type 4 is defined as diffusely infiltrating flat carcinoma in which ulceration is usually not a marked feature.

b Analysis for 18q LOH was performed as described in the Materials and methods section. Sixty-seven cases were informative for LOH assessment.

c Fisher's exact test.

d χ^2 test.

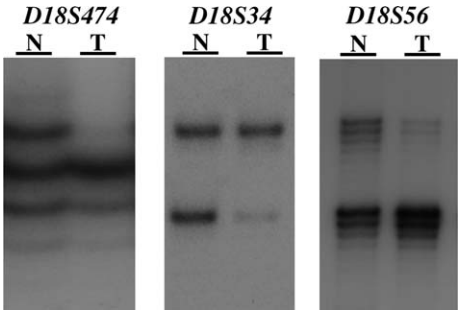

Fig. 2 – Loss of heterozygosity (LOH) on chromosome 18q using microsatellite markers. Assessment of LOH was assigned when a tumour allele showed at least a 50% reduction in the relative intensity of one allele in a tumour sample compared with the matched normal DNA. Lane *T*, DNA from the tumour; lane *N*, corresponding normal tissue.

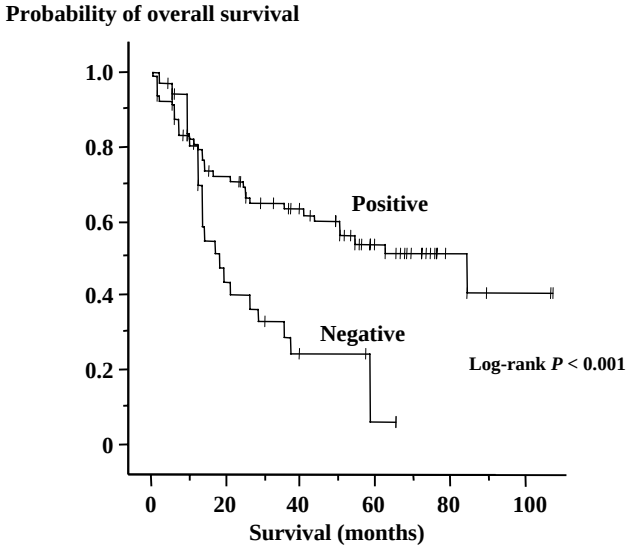

Fig. 3 – Probability of survival of resectable gastric cancer patients in relation to the desmoglein-2 expression of their tumour. A statistically significant difference in survival was observed between the Dsg2-positive and Dsg2-negative groups.

showed E-cadherin-negative staining, while only 16% (6/37) of intestinal-type cancers showed negative staining. E-cadherin expression had a significantly negative correlation with tumour differentiation ($P < 0.001$) and tumour macroscopic features ($P = 0.035$). E-cadherin expression was positive in 34 (45%) of 75 diffuse-type of gastric carcinomas. Forty-four percent (15 of 34) of diffuse-type cancers with normal E-cadherin expression showed Dsg2-negative staining, and 75% (56 of 75) of all diffuse-type cancers showed Dsg2 and/or E-cadherin-negative staining. No significant correlation was found between Dsg2 and E-cadherin expression.

3.3. *Relationship between desmoglein-2 expression and 18q LOH*

Fig. 2 shows typical examples of the LOH on 18q. Eighty cases were informative for LOH assessment. Seventeen (71%) of 24 cases with 18q LOH showed Dsg2-negative staining, while 45 (80%) of 56 cases without 18q LOH showed Dsg2-positive staining. Loss of Dsg2 expression was correlated significantly ($P = 0.001$) with LOH on the 18q locus (Table 1).

3.4. *Survival*

The prognosis of patients with Dsg2-negative tumours was significantly ($P < 0.001$) worse than that of those with Dsg2-positive tumours (Fig. 3); E-cadherin levels were not correlated significantly with patient survival. In univariate analysis (Table 2), Dsg2 ($P = 0.001$), tumour differentiation, *T* stage, peritoneal dissemination and lymph node metastasis were correlated significantly with patient survival. In multivariate analysis (Table 3), *T* stage, peritoneal dissemination, and lymph node metastasis, but not Dsg2 levels, were found to be independent prognostic factors ($P = 0.381$).

4. Discussion

In the present study, Dsg2 expression was found to be significantly decreased in diffuse-type gastric carcinoma, indicating that the loss of Dsg2 correlates with differentiation in gastric carcinomas. It has been suggested that desmosomal components may underlie differentiation in human endometrial carcinoma and murine squamous carcinoma.[20,21] Biedermann and colleagues have also reported that abnormal expression of Dsg2 is involved in the carcinogenesis of diffuse-type gastric carcinomas.[18] Desmosome formation correlates with the presence of both Dsg2 and plakoglobin.[22] Desmoplakin plays an important role in organizing the desmosomal cadherin-plakoglobin complex.[23] Desmosomal cadherins are linked directly to plakoglobin but not to β-catenin, and the restoration of plakoglobin has been shown to impact desmoglein expression in tumour cells.[1] The low expression of Dsg2 may be closely associated with epithelial cell–cell adhesion systems of desmosome.

We reported previously that loss of heterozygosity of the *Dsg2* locus, which exists at chromosome 18q12, might be associated with Borrmann type 4 gastric cancers.[15] Gastric carcinomas are classified morphologically as type 1 to 4 based on Borrmann's criteria.[19] Type 4 is defined as a diffusely infiltrating flat carcinoma in which ulceration is usually not a marked feature, while type 1 is defined as a polypoid tumour which is sharply demarcated from the surrounding mucosa.[19]

In the present study, Dsg2-negative staining was found to be significantly correlated with LOH on chromosome 18q, and a significant relationship between loss of Dsg2 expression with Borrmann type 4 gastric cancers was found. Loss of Dsg2 function may stimulate horizontal tumour infiltration in an invasive manner. The present study supports our previous hypothesis that loss of the *Dsg2* locus on chromosome 18q12 might be a candidate tumour suppressor locus in diffuse-type gastric cancers.

The loss of Dsg2 expression was found to have a significant correlation with peritoneal dissemination. Diffuse-type gastric cancer develops peritoneal metastasis more frequently

Table 2 – Univariate analysis with respect to overall survival in gastric cancer

Parameter	Odds ratio	95% confidence interval	P-value
Desmoglein-2 expression negative versus positive	0.392	0.229–0.672	0.001
E-cadherin expression negative versus positive	0.805	0.476–1.361	0.419
Desmoglein-2/E-cadherin expression negative versus positive	0.541	0.312–0.938	0.029
Morphological feature type 1/2 versus type 3/4	1.937	0.978–3.635	0.058
Differentiation diffuse type versus intestinal type	0.404	0.217–0.753	0.004
T stage T2 versus T3/T4	3.780	1.997–7.156	<0.001
Peritoneal metastasis negative versus positive	3.786	2.204–6.503	<0.001
Hepatic metastasis negative versus positive	1.550	0.557–4.315	0.402
Venous invasion negative versus positive	0.968	0.575–1.629	0.902
Lymph node metastasis negative versus positive	4.138	2.078–8.239	<0.001
Lymphatic invasion negative versus positive	1.469	0.760–2.841	0.253
Loss of heterozygosity on 18q negative versus positive	1.354	0.715–2.565	0.353

Table 3 – Multivariate analysis with respect to overall survival in gastric cancer

Parameter	Odds ratio	95% confidence interval	P-value
Desmoglein-2 expression negative versus positive	0.760	0.411–1.405	0.381
Morphologic feature type 1/2 versus type 3/4	1.326	0.654–2.686	0.434
Differentiation diffuse type versus intestinal type	0.849	0.417–1.727	0.651
T stage T2 versus T3/T4	2.028	0.951–4.325	0.067
Peritoneal metastasis negative versus positive	2.047	1.117–3.754	0.021
Lymph node metastasis negative versus positive	2.196	1.009–4.776	0.047

than intestinal-type gastric carcinomas. Tselepis and colleagues report that desmosomes have a suppressor function for tumour invasion and metastasis.[2] Peritoneal metastatic gastric cancer cells are thought to pass through several steps, such as invasion from the stomach to serosa and detachment from the primary tumour to the abdominal cavity. Loss of cell–cell adhesion following the decreased expression of Dsg2 may have high metastatic potential. Dsg2 expression was found to have a significantly negative correlation with T stage as depth of tumour invasion in the present study. Low Dsg2 expression might be associated with peritoneal metastatic ability, including invasion to the serosa, detachment from the primary tumour, and invasion into the peritoneum. Biedermann and colleagues report that Dsg2 expression has no correlation with T stage in gastric carcinomas in an analysis of 75 gastric carcinomas including 37 familial gastric carcinomas;[18] all 112 tumours in the present study were sporadic. Hereditary gastric tumours are known to have different histological and genetic features from those of sporadic carcinomas.[24] The high number of familial samples in Biedermann's study might be one of reasons for the differences between their results and ours.

Dsg2 expression was found to have a positive correlation with vascular invasion in the present study, while a correlation between loss of Dsg1 expression and vessel invasion has been observed in oesophageal cancer.[25] Tumour cell clusters are reported to be a potentially important mechanism for hepatic metastasis and penetration into the endothelium.[26,27] In the present study, 5 of 7 cases with liver metastasis were Dsg2-positive. These findings suggest that tumour cell clusters with venous invasion might be associated with hepatic metastasis in gastric carcinoma.

The loss of E-cadherin expression is believed to be one of the reasons for the characteristic histological features of diffuse-type gastric cancer.[16,17,28] The down-regulation of either α-catenin or E-cadherin plays a critical role in the disruption of cell adhesion in diffuse-type gastric carcinomas.[29] Accordingly, approximately 20–40% of diffuse-type gastric cancers show no abnormality of E-cadherin or α-catenin expression.[30,31] In the present study, E-cadherin expression was positive in 45% (34/75) of diffuse-type cancers, while 84% (31/37) of intestinal-type cancers showed positive expression. E-cadherin expression had a significantly negative correlation with tumour differentiation. Forty-four percent (15 of 34) of diffuse-type cancers with normal E-cadherin expression showed Dsg2-negative staining, and 75% of diffuse-type cancers showed Dsg2 and/or E-cadherin-negative staining. The present findings suggest that the loss of Dsg2 function might be one of the mechanisms of carcinogenesis of diffuse-type gastric cancers showing no abnormality in E-cadherin or α-catenin expression.

The prognosis of gastric cancer patients without Dsg2 expression was poor compared with that of those with Dsg2 expression, even though Dsg2 expression was not found to be an independent prognostic factor. Decreased function of Dsg2 may increase the infiltrative ability of cancer cells to develop peritoneal metastasis, which results in a poor prognosis. Thus, Dsg2 expression could be a useful marker for prognosis. Dsg2 expression showed a significant correlation with peritoneal dissemination in the present study, and peritoneal dissemination was correlated with patient survival in multivariate analysis. Dsg2 expression may depend on peritoneal dissemination in evaluating patient survival. The present findings address the reasons for which Dsg2 was not found to be an independent prognostic factor.

Conflict of interest statement

None declared.

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