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Serum levels of E-selectin, ICAM-1 and VCAM-1 in colorectal cancer patients: correlations with clinicopathological features, patient survival and tumour surgery

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Abstract

The serum concentrations of the cell adhesion molecules E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) were investigated in 63 patients with colorectal cancer and in 51 controls by an enzyme-linked immunosorbent assay (ELISA). Their relationship to clinicopathological variables and patient survival and changes in their levels after surgery were examined. Colorectal cancer patients showed significantly higher serum levels of E-selectin, ICAM-1 and VCAM-1 compared with healthy controls. There was a significant association between the serum levels of these molecules, disease stage and the presence of both lymph node and distant metastases. Both ICAM-1 and VCAM-1 levels correlated with serum E-selectin and carcinoembryonic antigen (CEA) levels. Serum levels of all three molecules decreased significantly after radical resection of the tumour. Elevated pre-operative E-selectin, ICAM-1 and VCAM-1 levels were significant prognostic factors, although not independent of stage, for patient survival. These findings suggest that serum concentrations of E-selectin, ICAM-1 and VCAM-1 may reflect tumour progression and metastasis. Since these markers are linked to CEA levels, it is uncertain whether their measurement will prove cost-effective in colorectal cancer management.

Keywords: Cell adhesion molecule; E-selectin; ICAM-1; VCAM-1; Surgery; Prognosis; Survival

1. Introduction

Tumour growth and the formation of metastases is a multistep process involving complex interactions between tumour cells and the vascular endothelium [1]. These interactions are mediated by several cell-surface adhesion receptors including the selectins, integrins and immunoglobulin-like cell adhesion molecules [2].

E-selectin is expressed on activated endothelial cells and may bind cells expressing specific ligands containing sialyl-Lewis residues. Experimental studies have suggested that the efficiency of the E-selectin-mediated binding of colonic carcinoma cells to human endothelium correlates with tumour progression and the formation of haematogenous metastases [3–5]. Intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are both members of the immunoglobulin superfamily of adhesion molecules. ICAM-1 is constitutively expressed by endothelial cells and by some leucocytes and serves as a ligand for the leucocyte β_2 integrin receptors, lymphocyte function associated antigen-1 (LFA-1) and Mac-1 [6]. VCAM-1 is found mainly on activated endothelial cells serving as a ligand for the $\alpha_4\beta_1$ integrin receptor, VLA-4 [7]. Both ICAM-1 and VCAM-1, like E-selectin, are expressed on endothelial cells of small blood vessels adjacent to colorectal cancer cell nests [8–10]. Their expression is upregulated by cytokines produced by the tumour and soluble forms of all three adhesion molecules have been detected in the supernatants of cytokine-activated endothelial cells and in the culture media of colonic carcinoma cell lines [11,12]. Elevated serum concentrations of E-selectin, ICAM-1 and VCAM-1 have only recently been described in patients with solid tumours, including

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colorectal cancer [13–15], melanoma [16], breast [17,18] and gastric cancer [19]. These serum levels correlate in many studies with tumour stage and the development of metastases, although their impact on patient survival is at present unclear.

In this study, we evaluated the serum concentrations of E-selectin (sE-selectin), ICAM-1 (sICAM-1) and VCAM-1 (sVCAM-1) in colorectal cancer patients and assessed their relationship to clinicopathological features and patient survival, as well as their changes after surgical removal of the tumour.

2. Patients and methods

63 consecutive patients with newly diagnosed and histologically-confirmed primary colorectal cancer were included in this prospective study. There were 33 men and 30 women with a median age of 70 years (range 47–90 years). No patient had received chemotherapy, irradiation or blood transfusion prior to surgery. Tumour staging was performed according to the Dukes' and TNM classifications. There were 13 patients with Dukes' stage A ($T_{1\text{-}2}N_0M_0$), 21 patients with Dukes' stage B ($T_{3\text{-}4}N_0M_0$) and 16 patients with Dukes' stage C ($T_xN_1M_0$) disease. 13 patients with distant metastases were classified as having Dukes' stage D ($T_xN_xM_1$) disease. These included 8 patients with liver metastases, 3 patients with peritoneal dissemination and 2 patients with both liver metastases and peritoneal dissemination. Patients were followed prospectively and the dates and causes of death recorded. The median follow-up was 30 months (range 1–50 months).

The control group consisted of 51 age and sex-matched healthy volunteers (median age 68 years, range 49–85 years; 28 men and 23 women). The absence of disease was assessed by clinical history, physical examination and routine laboratory tests including liver and renal function tests.

2.1. Blood samples and assays

Peripheral venous blood samples were drawn into sterile glass tubes (Vacutainer, Becton Dickinson, Plymouth, UK) in the morning (8.00–9.00 h) after an overnight fast. Samples were allowed to coagulate at room temperature for 30 min, centrifuged at 2000*g* for 10 min, and serum was separated, aliquoted and stored at −70 °C until assay. Serum samples from colorectal cancer patients were collected preoperatively and 7 days following surgery.

Serum E-selectin and VCAM-1 concentrations were determined using a solid phase, enzyme-linked immunosorbent assay (ELISA) designed to measure soluble levels of E-selectin and VCAM-1 in cell culture supernatant, serum and plasma (Parameter, R&D Systems, Minneapolis, MN, USA). The assays employ the quantitative sandwich enzyme immunoassay technique using recombinant human E-selectin and VCAM-1 with antibodies raised against the recombinant proteins, respectively. Their sensitivity was 1 ng/ml for sE-selectin and 2 ng/ml for sVCAM-1. Serum levels of ICAM-1 were also measured by an ELISA using a commercially available kit designed for the quantitative measurement of human sICAM-1 (Cellfree, Endogen, Woburn, MA, USA) with a sensitivity of 0.3 ng/ml.

Serum carcinoembryonic antigen (CEA) levels were determined as part of the pre-operative evaluation simultaneously with blood sampling using a commercial ELISA assay (Tosoh, Tokyo, Japan).

2.2. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) statistical software package. Data were tested for normality and were found to be non-normally distributed. Accordingly, all data are presented as medians (interquartile range). The Kruskal–Wallis analysis of variance (ANOVA), the Mann–Whitney U test and the Wilcoxon rank test were used to evaluate differences between multiple groups, unpaired and paired observations, respectively. Correlations were evaluated using the Spearman rank test. Survival curves were obtained by the Kaplan–Meier method and comparisons were made with the log-rank test. The Cox proportional hazards regression model was used for the multivariate analysis after univariate analysis had defined the relevant prognostic variables. Significance was presumed at $P < 0.05$.

3. Results

3.1. Serum levels of cell adhesion molecules in healthy controls and colorectal cancer patients

All three adhesion molecules were detectable in all control subjects and colorectal cancer patients. Preoperative serum E-selectin, ICAM-1 and VCAM-1 levels in patients with colorectal cancer were significantly higher than those of healthy controls (Table 1). There were no significant differences within either the control or the cancer population between males and females or according to age.

The relationships between serum levels of cell adhesion molecules and clinicopathological variables are shown in Table 2. There was a significant association between disease stage and sE-selectin ($P = 0.03$), sICAM-1 ($P = 0.00005$) and sVCAM-1 levels ($P = 0.00008$), respectively. When patients with metastatic disease (Dukes' stages C and D) were compared with those with tumours limited to the bowel wall (Dukes' stages A and

B), they were found to have significantly higher concentrations of sE-selectin (47 (39–68) versus 37.5 (29–49) ng/ml, respectively; $P=0.02$), sICAM-1 (365 (285–508) versus 225 (165–293) ng/ml, respectively; $P=0.00002$), and sVCAM-1 (696 (563–846) versus 434 (283–569) ng/ml, respectively; $P=0.00003$).

Patients with lymph node metastases had significantly higher sE-selectin ($P=0.02$), sICAM-1 ($P=0.00002$) and sVCAM-1 ($P=0.00003$) levels when compared with those without lymph node involvement.

The patients with liver metastases also had significantly higher sE-selectin ($P=0.006$), sICAM-1 ($P=0.00005$) and sVCAM-1 ($P=0.002$) levels in comparison with patients without liver metastases.

There were no significant correlations between the serum levels of the studied cell adhesion molecules, tumour location, degree of differentiation and tumour extension through the bowel wall (T class).

Serum levels of E-selectin correlated significantly with both sICAM-1 ($r=0.36$, $P=0.004$) and sVCAM-1 ($r=0.3$, $P=0.017$) levels. There were also significant associations between pre-operative serum CEA concentrations and both sICAM-1 ($r=0.29$, $P=0.018$) and sVCAM-1 ($r=0.46$, $P=0.0002$) levels.

Table 1
Circulating levels of cell adhesion molecules in the serum of healthy controls and patients with colorectal cancer

	Controls ($n=51$)	Patients ($n=63$)	Significance
sE-selectin (ng/ml)	39.6 (33.6–44.8)	44 (32–55.6)	0.039[a]
sICAM-1 (ng/ml)	203 (138–245)	285 (195–365)	0.00005[a]
sVCAM-1 (ng/ml)	413 (348–516)	555 (389–703)	0.0004[a]

sICAM-I, serum intercellular adhesion molecule-1; sVCAM-1, serum vascular cell adhesion molecule-1.

Values are medians (interquartile range).

[a] Statistically significant differences; patients versus controls (Mann-Whitney U test).

3.2. The effect of surgery on the serum levels of E-selectin, ICAM-1 and VCAM-1

Radical resection of the primary tumour was performed in 47 patients whereas 16 patients had a non-curative operation. 13 patients with distant metastases had palliative resection of the primary tumour and three patients with locally advanced unresectable tumours underwent palliative bypass surgery for obstructive presentation.

Seven days following radical tumour resection, there was a significant decrease in the serum levels of E-selectin (33.8 (29–44) versus 41.6 (32–50) ng/ml, respectively;

Table 2
Relationship between serum levels of E-selectin, ICAM-1 and VCAM-1 and pathological variables in colorectal cancer patients[a]

	sE-selectin (ng/ml)	sICAM-1 (ng/ml)	sVCAM-1 (ng/ml)
Tumour location			
Colon ($n=45$)	44 (35.4–55.6)	283 (206–365)	569 (392–703)
Rectum ($n=18$)	41.5 (32–51.8)	292 (195–384)	485 (389–689)
Tumour differentiation			
Well ($n=5$)	32 (29.8–39.6)	298 (206–306)	467 (432–569)
Moderate ($n=44$)	45.3 (33.7–53.8)	271 (172–326)	527 (374–673)
Poor ($n=14$)	45 (39.6–68)	342 (278–392)	664 (563–859)
Dukes' stage			
A ($n=13$)	46 (32–49)	238 (206–292)	555 (467–592)
B ($n=21$)	36 (29–48)	212 (162–297)	392 (276–473)
C ($n=16$)	42.8 (34.7–54)	292 (273–416)	645 (494–725)
D ($n=13$)	52 (46–76)*	498 (365–625)*	746 (627–864)*
Tumour category			
pT_1 ($n=3$)	32 (22–66.8)	206 (195–238)	532 (467–748)
pT_2 ($n=12$)	47 (41.5–56.6)	261 (184–295)	562 (445–606)
pT_3 ($n=26$)	38.5 (33.4–50)	284 (180–327)	544 (392–725)
pT_4 ($n=22$)	46.5 (32–58)	322 (241–483)	530 (386–726)
Lymph node metastases			
pN_0 ($n=34$)	37.5 (29–49)	225 (165–293)	434 (283–569)
$pN_{1\ or\ x}$ ($n=29$)[b]	47 (39–68)**	365 (285–508)**	696 (563–846)**
Distant metastases			
pM_0 ($n=50$)	40.6 (32–50)	267 (180–306)	514 (389–620)
pM_1 ($n=13$)	52 (46–76)**	498 (365–625)**	746 (627–864)**

ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.

Values are medians (interquartile range).

[a] Statistically significant differences: * Kruskal–Wallis ANOVA; ** Mann–Whitney U test.

[b] Including three cases not undergoing resection where N status was unknown.

$P = 0.001$), ICAM-1 (207 (157–294) versus 265 (165–298) ng/ml, respectively; $P = 0.01$) and VCAM-1 (432 (297–566) versus 526 (389–620) ng/ml, respectively; $P = 0.0002$).

In contrast, postoperative levels of all adhesion molecules in patients undergoing non-curative resection or palliative bypass did not differ from the corresponding preoperative levels.

3.3. Correlations between the serum levels of the cell adhesion molecules and patient survival

Elevated serum levels of the studied cell adhesion molecules were defined as being greater than the 95th percentile values in the healthy control group. This resulted in a cut-off value of 52, 336 and 638 ng/ml for sE-selectin, sICAM-1 and sVCAM-1, respectively. Using these cut-off levels, elevated sE-selectin, sICAM-1 and sVCAM-1 levels were found in 15 (24%), 17 (27%) and 19 (30%) of the patients, respectively.

During the study, 27 patients died of colorectal cancer and 36 patients remained alive, 5 of them with documented tumour recurrence. Univariate analysis showed that the degree of differentiation, Dukes' stage, depth of bowel wall invasion, lymph node involvement, presence of distant metastases, serum CEA levels, sE-selectin, sICAM-1 and sVCAM-1 levels were all significant factors affecting overall survival (Table 3). Log-rank analysis confirmed elevated pre-operative sE-selectin, sICAM-1 and sVCAM-1 levels as correlating with poor overall survival (Fig. 1). Multivariate regression analysis revealed that only Dukes' stage remained as an independent prognostic factor for cancer-specific survival (data not shown).

4. Discussion

In this study, colorectal cancer patients showed significantly higher serum levels of the cell adhesion molecules E-selectin, ICAM-1 and VCAM-1 when compared with healthy controls. There was a strong association between the serum levels of all three adhesion molecules, disease stage and the presence of both lymph node and visceral metastatic disease. Both sICAM-1 and sVCAM-1 levels correlated with sE-selectin, and with pre-operative concentrations of serum CEA. Serum levels of these molecules fell significantly if resection was carried out for cure and there was an association between pre-operative sE-selectin, sICAM-1 and sVCAM-1 and cancer-specific survival, although this was not maintained in the multivariate analysis.

Previous studies have demonstrated elevated pre-operative sICAM-1 and sVCAM-1 levels in colorectal cancer patients [13,14], whereas results regarding sE-selectin are more variable with some reports showing elevated levels of sE-selectin in colorectal cancer patients [15,20], whilst others have failed to detect such a difference [13]. In our study, sE-selectin correlated significantly with both sICAM-1 and sVCAM-1 suggesting that their elevation may be a co-ordinated event in tumour progression and metastasis since it has been shown *in vitro* that soluble E-selectin will upregulate ICAM-1 expression in a range of human tumour cell lines [21].

Serum levels of the soluble adhesion molecules fell significantly after resection for cure, but not when surgery was palliative. We believe that this is the first time in the reported literature that monitoring of serum concentrations of adhesion molecules has been suggested as a possible marker for potentially curative colorectal cancer resection. The cellular source, mechanism of release and the structure of these soluble adhesion molecule isoforms are at present unknown. It is likely that soluble products are derived from a range of sources including enzymatic cleavage from endothelial, leucocyte and tumour cell surfaces, perhaps influenced by the intra-tumoral cytokine environment. It is accepted, however, that measurement of these molecules may not

Table 3
Univariate analysis for predictors of survival in 63 patients with colorectal cancer

Variable	HR	95% CI	*P* value
Age	1.03	0.98–1.08	0.25
Sex (Male versus Female)	0.49	0.22–1.12	0.09
Tumour location (Rectum versus Colon)	1.2	0.52–2.78	0.65
Differentiation (Well versus Moderate versus Poor)	3.59	1.72–7.45	0.0006
Dukes' Stage (A versus B versus C versus D)	4.24	2.34–7.67	0.00001
T Class (T_1 versus T_2 versus T_3 versus T_4)	2.04	1.2–3.47	0.008
Nodal status (N_0 versus N_1)	7.01	2.61–18.77	0.0001
Distant metastases (M_0 versus M_1)	17.46	5.88–51.86	0.00001
CEA (Elevated versus Normal)	7.42	2.53–21.72	0.0003
sE-selectin (Elevated versus Normal)	2.81	1.28–6.2	0.01
sICAM-1 (Elevated versus Normal)	3.97	1.82–8.67	0.0005
sVCAM-1 (Elevated versus Normal)	4.5	2.04–9.9	0.0002

HR, Hazard ratio; CI, Confidence interval; sICAM-1, serum intercellular adhesion molecule-1; sVCAM-1, serum vascular cell adhesion molecule-1; CEA, carcinoembryonic antigen.

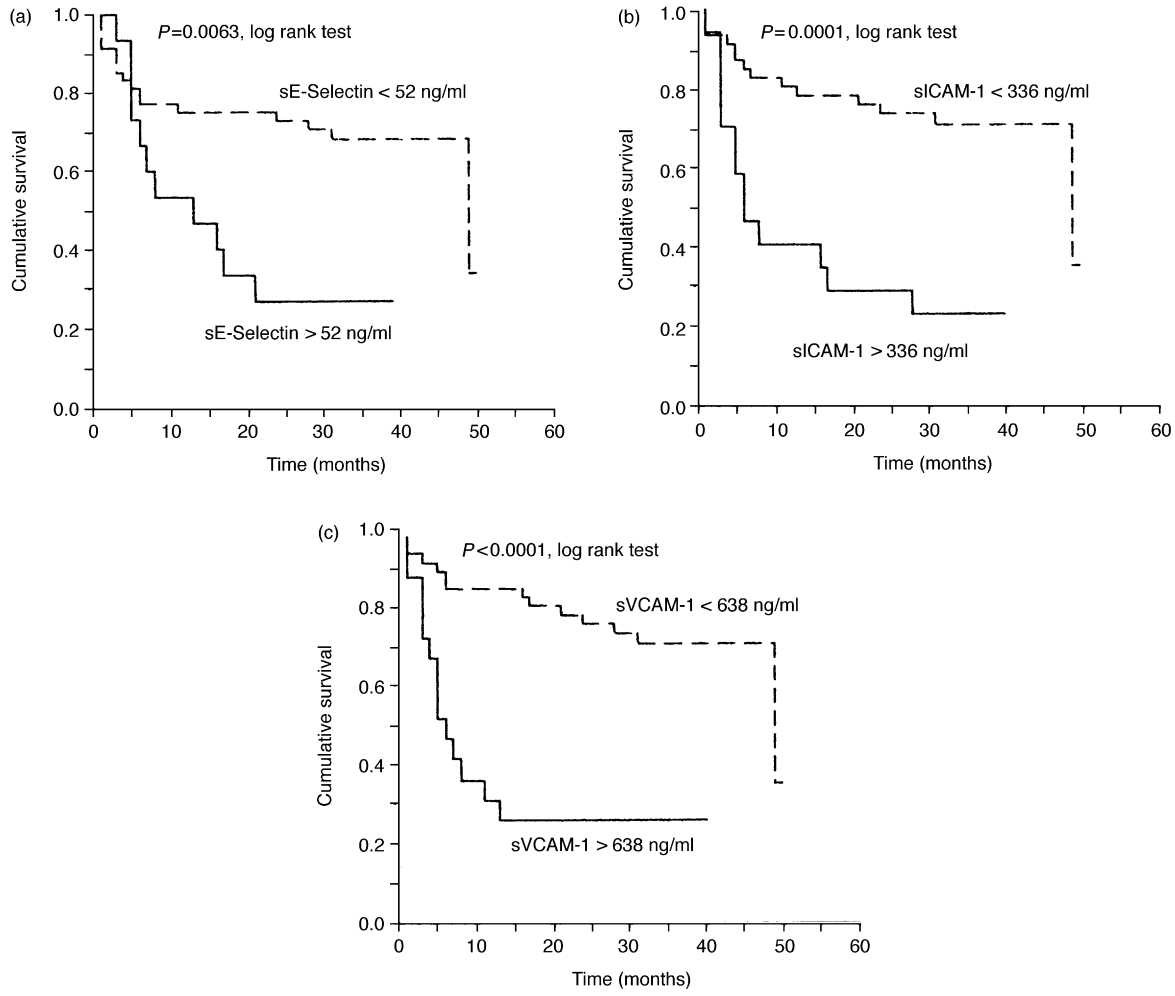

Fig. 1. Kaplan–Meier survival curves showing a significantly higher survival rate in patients with non-elevated (- - -) compared with those with elevated (—) serum concentrations of (a) E-selectin, (b) intercellular adhesion molecule-1 (ICAM-1). and (c) vascular cell adhesion molecule-1 (VCAM-1).

necessarily be more cost-effective than conventional CEA measurement, given the relatively low efficacy of serum screening for potentially resectable recurrence during colorectal cancer follow-up [22].

Our findings that pre-operative serum levels of adhesion molecules affect survival in colon cancer have not been previously reported. They are consistent with studies showing that pre-operative soluble adhesion molecule levels are prognostic indicators for cancer-specific survival in other solid tumours, such as cutaneous malignant melanoma [16], gastric [19] and breast cancer [17]. However, other tumours like non small-cell lung carcinoma have shown an inverse relationship between prognosis and preoperative levels of soluble adhesion molecules [23].

In our study, preoperative levels of sE-selectin, sICAM-1 and sVCAM-1 were not found to be independent prognostic variables affecting survival in colorectal cancer in the multivariate analysis. The association in colorectal cancer between immunohistochemical adhesion molecule expression and CD3-positive leucocyte infiltration suggests an important role for these molecules in the host immune response [24]. There appears, however, to be different relationships (with tumour progression) for the tissue expression of the adhesion molecules and their circulating soluble counterparts. ICAM-1 expression in the tumour microvasculature favours cytotoxic lymphocyte trafficking towards the tumour and facilitates transmigration of monocytes and T lymphocytes across the endothelium, enhancing tumour angiogenesis [3]. Circulating ICAM-1, on the other hand, interferes with natural killer and lymphocyte-activated killer cell reactivity against tumour cells [25,26] so that shedding of adhesion molecules by endothelial or tumour cells can block counter-ligands on immunocompetent recognition lymphocytes, thereby promoting metastasis development [27]. This paradoxical effect between tissue and soluble adhesion molecule function may explain the lack of significance in multivariate analysis on the colorectal cancer outcome. An improved understanding of the mechanisms of membrane shedding of these adhesion mediators,

their effect on the host immune response and the role of angiogenesis inhibitors on their expression is required to elucidate their place in colorectal cancer progression.

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