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Serum levels of soluble ICAM-1 and VCAM-1 predict pre-clinical cancer

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Abstract

To investigate whether serum levels of soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) were related to first stage cancer before diagnosis of cancer, we compared serum levels of these adhesion molecules between pre-clinical cases and controls using a nested case-control study method. Cancer cases were recruited from a cohort database of 1465 participants who completed a baseline questionnaire and provided blood samples, and were followed up from 1989 to 2003. They consisted of 15 individuals who died of cancer and 31 individuals newly diagnosed with cancer during the follow-up period. Controls were subjects who did not suffer from cancer, cerebral apoplexy, diabetes mellitus, liver disease, or myocardial infarction during the follow-up period. Using commercially available enzyme-linked immunosorbent assay (ELISA) kits, we showed that serum levels of sVCAM-1, but not sICAM-1 were elevated in cases with pre-clinical or early cancer. We suggest that elevated serum levels of sVCAM-1 might serve as a possible marker for detecting pre-clinical or early cancer.

Keywords: Gastric cancer; Intercellular adhesion molecule-1; Large intestine cancer; Nested case-control study; Vascular cell adhesion molecule-1

1. Introduction

Intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) are members of the immunoglobulin super-family of adhesion molecules. Both participate in adhesion between cells [1]. Soluble forms of ICAM-1 (sICAM-1) and VCAM-1 (sVCAM-1) have been previously identified [2,3]. Elevated serum levels of sICAM-1 and sVCAM-1 have recently been described in patients with gastric cancer [4,5], colorectal cancer [6–8], breast cancer [9,10], melanoma [11], and leukaemia [12]. These adhesion molecules significantly correlated with tumour stage and the development of metastases of gastric cancer [5], colorectal cancer [8], and breast cancer [10]. In gastric cancer [5] and colorectal cancer [8], sICAM-1 and sVCAM-1 serum levels decreased significantly after radical resection of the tumour. These previous reports investigated the levels of adhesion molecules in blood samples taken from patients after being diagnosed with cancer. No study has documented serum levels of sICAM-1 and sVCAM-1 in subjects with pre-clinical cancer. It is therefore questionable whether elevated serum levels of sICAM-1 and sVCAM-1 predict the disease risk of cancer. To investigate this, we performed a comparison of serum sICAM-1 and sVCAM-1 levels between cases of pre-clinical cancer and controls using a nested case-control study method.

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2. Materials and methods

2.1. Study population

The study protocol was based on that of the Japan Collaborative Cohort Study for the Evaluation of Cancer Risk sponsored by Monbusho (JACC Study) [13]. Study participants were residents (age: 40–79 years old) of a rural community in west Tottori Prefecture, Japan. In 1989, 1465 subjects who underwent health check-ups sponsored by their municipality were asked to donate blood samples and to participate in a self-administered baseline questionnaire.

Investigation purposes were sufficiently explained to each subject, then written informed consent was obtained. The questionnaire included questions regarding histories for 10 diseases (apoplexy, hypertension, myocardial infarction, renal and liver diseases, gallstone/cholecystitis, diabetes mellitus, peptic ulcer, pulmonary tuberculosis and cancer) and lifestyle factors such as educational status, smoking habits, alcohol consumption, dietary habits and physical activities. Medical history reconfirmed that there was no disease in the health check-ups. In the health check-ups, urinalysis (urine protein, urine sugar, urobilinogen, occult blood), blood examination (Hb: hemoglobin, RBC: red blood cell, MCH: mean corpuscular hemoglobin, TC: total cholesterol, GOT: glutamate–oxaloacetate transaminase, GPT: glutamate–pyruvate transaminase), and sphygmomanometry were carried out. All subjects were followed up until the end of 2003. The follow-up period was 14 years. Residential and survival status was confirmed by searching official residential rosters for changes in address or death, and death certificates were reviewed with regards to the cause and date of death with permission from the Director-General of the Prime Minister's Office. Cancer clinical history at baseline was investigated using both the self-administered baseline questionnaire and regional tumour registry. Classification of the cause of death followed the 10th edition of the International Classification of Disease (ICD-10). A second (interim) questionnaire survey on general health condition, exercise, smoking habits, and alcohol intake of the subject was conducted in 1994.

2.2. Case ascertainment and control selection

Investigations were performed using the nested case-control study method. Subjects who suffered from cancer, cerebral apoplexy, diabetes mellitus, liver disease, or myocardial infarction at baseline were excluded from the analysis. Furthermore, to exclude advanced cancer disease from investigations, cases who died within five years of follow-up were removed from the cancer cases. Cancer cases consisted of 15 individuals (8 men, 7 women) who died as a result of cancer, and 31 individuals (12 men, 19 women) newly diagnosed with cancer during the follow-up period. A 1:2 ratio of cancer cases to controls was used in this study. Controls were subjects who did not suffer from cancer and who reported no histories of cerebral apoplexy, diabetes mellitus, liver disease, or myocardial infarction at the baseline (1989) and interim (1994) surveys. Cases were matched individually according to gender, age (±4 years) and smoking habits (non-smoker or smoker).

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Tottori University (No. 399, 2004).

2.3. Blood analysis

Peripheral venous blood samples were drawn into sterile glass tubes in the morning (9:00–10:00 AM) after an overnight fast. Samples were allowed to coagulate at room temperature for 30 min then centrifuged at 2500 g for 10 min. The serum was separated and stored at −70 °C until analysis. Before analysis, samples were thawed slowly and mixed gently. Serum sICAM-1 and sVCAM-1 concentrations were determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Bender MedSystems, Vienna, Austria) according to procedures recommended by the manufacturer. The optical density of each well was determined with the Microplate Reader (Bio-Rad Laboratories, California, USA) set to 450 nm; wave correction was set to 630 nm. Each serum sample concentration was calculated automatically from standard curves. Each serum sample was tested in duplicates. The sensitivity of the sICAM-1 assay was 0.5 ng/ml, the inter-assay coefficient of variance was 7.8% and the intra-assay coefficient of variation was 7.5%. The sensitivity of the sVCAM-1 assay was 0.9 ng/ml, the inter-assay coefficient of variance was 5.2% and the intra-assay coefficient of variation was 4.4%.

2.4. Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Science (SPSS) statistical software package. Data presented were means ± SD. Comparisons between the two groups were made using the Student's t test or the χ^2 test. P values less than 0.05 were considered significant (two-tailed).

3. Results

Baseline characteristics of the cancer cases and controls are shown in Table 1. Mean age of the cancer group and control group are 60 ± 6 (61.9 ± 5.2 men, 59.8 ± 8.3 women) and 60.7 ± 7.1 (60.1 ± 4.8 men, 59.7 ± 7.6 women) years old, respectively. There were