

Serum Levels of CA15-3, KL-6 and BCA225 Are Positively Correlated with Each Other in the General Population

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Abstract. *Background:* Carbohydrate antigen 15-3 (CA15-3), Kerbs von den Lungen (KL-6) and breast cancer antigen 225 (BCA225) are widely used tumor markers for breast and lung cancer respectively. *Patients and Methods:* We analyzed 460 Japanese volunteers for 99 items on blood examination including 27 serum tumor markers. Correlations between 27 tumor markers and the other items were statistically analyzed. *Results:* Positive correlations were identified between CA15-3 vs. KL-6, CA15-3 vs. BCA225, and KL-6 vs. BCA225, with correlation coefficients of 0.84, 0.86, and 0.79, respectively. *Conclusion:* This is the first report to show a positive correlation among these markers in the general population. All of these are recognized as belonging to the mucin family, and this might be the reason for the positive correlation.

Serum tumor markers play an important role in medical evaluation of patients with malignancies (1). Usually, these markers are used to predict postoperative relapse of cancer. Some researchers are investigating the use of these markers for the prediction and identification of malignancies (2, 3).

Since 2006, we have been investigating a newly designed health check system using a computer interface. In this system, there are 99 items of blood examinations including 27 serum tumor markers (4). To date, the results of blood examinations from 460 clients have been accumulated, and analyzed by computer. In this study, we analyzed these data for a significant correlations.

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Patients and Methods

After obtaining informed consent, 460 Japanese individuals (male 305/ female 155) were recruited as volunteers. Their mean ages were 53.1 ± 10.6 years (male) and 52.1 ± 13.7 years (female). A total of 99 items were checked on blood examinations (Table I), and the results were statistically analyzed by Pearson's product-moment correlation coefficient. All statistical analyses were performed using the statistical package Microsoft Excel version 2004 for Macintosh.

Results

Correlation study was performed between the tumor markers and the other parameters assessed. Significant correlation was shown among three tumor markers: carbohydrate antigen (CA) 15-3, Kerbs von den Lungen (KL) -6, and breast cancer antigen (BCA) 225 (Figures 1-3). Correlation coefficients for CA15-3 vs. KL-6, CA15-3 vs. BCA225 and KL-6 vs. BCA225 were 0.84 ($p=2.2 \times 10^{-125}$), 0.86 ($p=3.2 \times 10^{-137}$), and 0.79 ($p=2.7 \times 10^{-97}$), respectively.

Discussion

CA15-3, KL-6 and BCA225 were included in our study based on research to establish a new health check system for early diagnosis of cancer, prevention of life-style diseases, and prediction of future diseases. Based on this study, serum CA15-3, KL-6 and BCA225 levels showed a positively correlated result. There is a report of a positive correlation between serum CA15-3 and KL-6 in patients with interstitial pneumonia associated with collagen diseases (5). Thus, this is the first report to show a positive correlation among CA15-3, KL-6 and BCA225 in the general population.

CA15-3 is one of the first identified prognostic factors and the most widely used serum marker in breast cancer (6-8). CA15-3 is a member of a polymorphous group of highly glycosylated proteins, and is recognized by two murine monoclonal antibodies: 115D8, generated against milk fat globulin membranes, and DF3, generated against a membrane extracted

Table I. List of blood examination parameters.

Blood count (9)	Tumor marker (27)
White blood cell (WBC)	Adenosine deaminase (ADA)
Leukocyte fractionation	Sialic acid (neuraminic acid)
Red blood cell (RBC)	Carbohydrate antigen 125 (CA125)
Hemoglobin (Hb)	Carbohydrate antigen 15-3 (CA15-3)
Hematocrit (Ht)	Carbohydrate antigen 19-9 (CA19-9)
Platelets (PLT)	Carbohydrate antigen 72-4 (CA72-4)
Mean corpuscular volume (MCV)	Squamous cell carcinoma antigen (SCC)
Mean corpuscular hemoglobin (MCH)	Thymidine kinase activity (TK)
Mean corpuscular hemoglobin concentration (MCHC)	Hyaluronic acid
Liver function (16)	Sialyl Lewis X-i antigen (SLX)
Total protein	KL-6 antigen (KL-6)
Albumin	β 2-Microglobulin serum (BMG)
Thymol turbidity test (TTT)	Cross-linked carboxyterminal telopeptide of type I collagen (I CTP)
Zinc sulfate turbidity test (ZTT)	Carcinoembryonic antigen (CEA)
Creatine kinase (CK)	Basic fetoprotein serum (BFP)
Creatine kinase, cardiac muscle (CK-MB)	Breast cancer antigen 225 (BCA225)
Aspartate aminotransferase (AST)	Sialyl Tn antigen (STN)
Alanine aminotransferase (ALT)	NCC-ST-439
Lactate dehydrogenase (LDH)	Prostate-specific antigen (PSA)
Alkali phosphatase (ALP)	Gamma-seminoprotein (gamma-Sm)
Gamma-glutamyl transpeptidase (GTP)	Tissue polypeptide antigen (TPA)
Cholinesterase (ChE)	Cytokeratin 19 fragment (CYFRA)
Leucine aminopeptidase (LAP)	Immunosuppressive acidic protein (IAP)
Total bilirubin (T-Bil)	Neuron-specific gamma-enolase (NSE)
Direct bilirubin (D-Bil)	Pro-gastrin releasing peptide (Pro GRP)
Indirect bilirubin (I-Bil)	Protein induced by vitamin K absence or antagonist (PIVKA-II)
Pancreas function (2)	Total acid phosphatase (ACP)
Amylase (AMY)	Autoimmune factor (4)
Lipase	Complement, total
Kidney function (3)	Third components of complement (C3)
Creatinine (Cre)	Fourth components of complement (C4)
Uric acid (UA)	Rheumatoid factor (RF)
Blood urea nitrogen (BUN)	Immunology (9)
Fat metabolism (12)	C-reactive protein quantitative (CRP)
Triglyceride (TG)	Epstein-Barr virus IgG
Phospholipid (PL)	Epstein-Barr virus EBNA
Non-esterified fatty acid (NEFA)	T-cell CD2 percentage
Total cholesterol (T-cho)	T-cell CD2 number
Lipoprotein electrophoresis	B-cell CD20 percentage
High-density lipoprotein cholesterol (HDL)	B-cell CD20 number
RLP cholesterol	Lymphocyte blastogenesis, phytohemagglutinin mitogens (PHA)
Lipoprotein (a)	Cell immunity Stimulation Index
Apolipoprotein A1 (Apo A1)	Gastric function (4)
Apolipoprotein B (Apo B)	Pepsinogen I (PG I)
Apolipoprotein E (Apo E)	Pepsinogen II (PG II)
Apolipoprotein B/A1 ratio	Pepsinogen I/II ratio (PG I/II)
Serum electrolyte (6)	<i>Helicobacter pylori</i> IgG antibody (HRP IgG)
Sodium (Na)	Iron metabolism (4)
Potassium (K)	Iron serum (Fe)
Chloride (Cl)	Total iron-binding capacity (TIBC)
Magnesium (Mg)	Ferritin
Calcium (Ca)	Ferritin/Fe ratio
Phosphate, inorganic (P)	Glucose metabolism (2)
Vitamin (1)	Glucose (Glu)
Vitamin A (retinol)	Hemoglobin A1c (HbA1c)

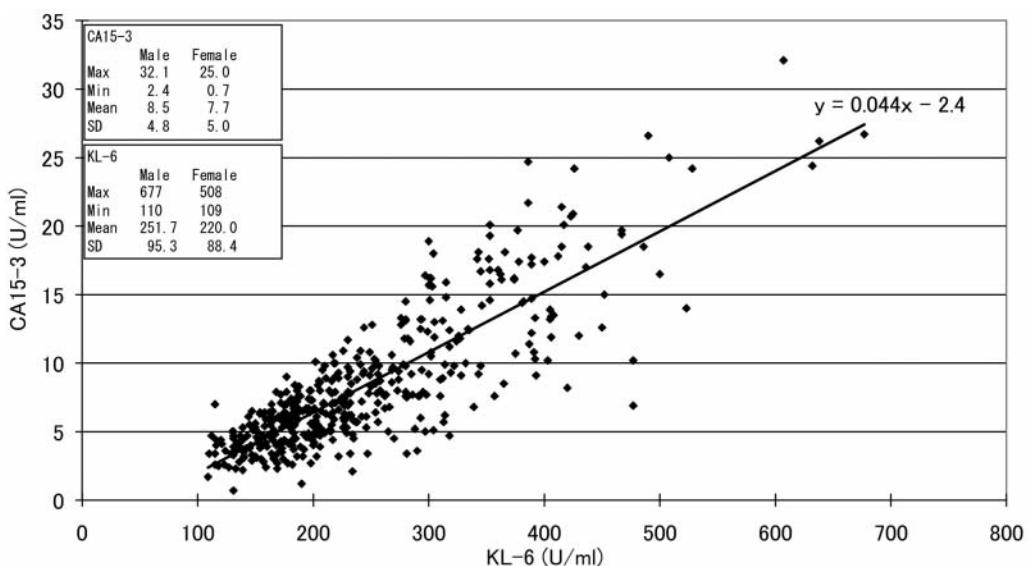


Figure 1. CA15-3 vs. KL-6 (correlation coefficient=0.84).

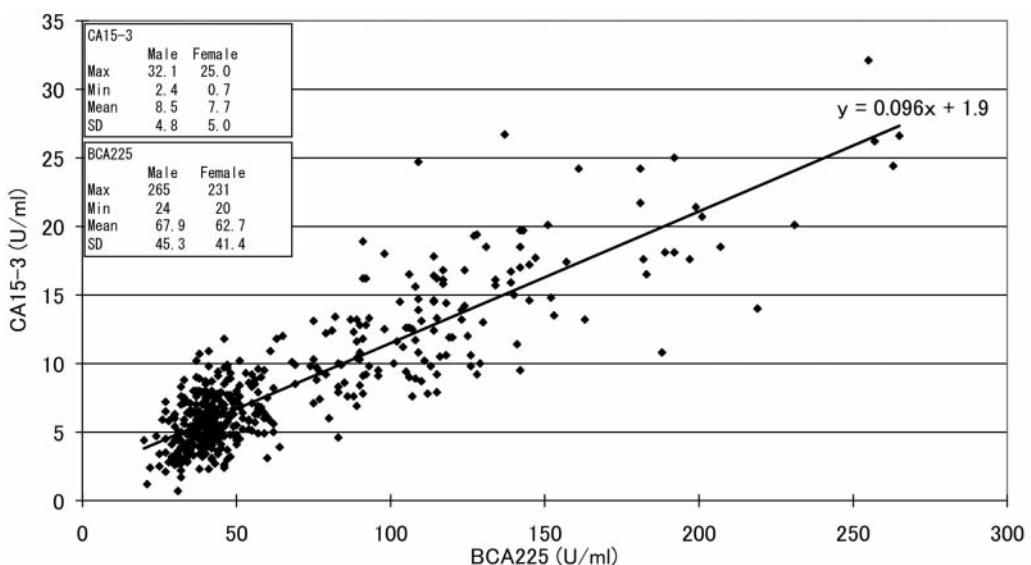


Figure 2. CA15-3 vs. BCA225 (correlation coefficient=0.86).

from human metastatic breast carcinoma (9, 10). BCA225 is a glycoprotein secreted by the T47D breast carcinoma cell line and recognized by monoclonal antibodies CU18 and CU46. BCA225 is regarded as useful tumor marker alone and in combination with CA15-3 for detecting the recurrence of breast cancer. KL-6 is a high molecular weight glycoprotein classified in the category of cluster 9 mucin-1 (MUC1) of lung tumor and differentiation antigens according to the finding of immunohistochemical and flow cytometric studies (11, 12).

Both epitopes of CA15-3 and KL-6 exist in different positions of MUC1 expressed on the surface of various

epithelial cells (13). MUC1, classified as a member of the mucin family, is a high molecular weight glycoprotein rich in O-glycosylated serine and threonine residues (14). The up-regulated expression of MUC1 has been noted in breast and lung adenocarcinomas (14). Monoclonal antibody for BCA225 is the same as that recognizing CA15-3, and KL-6, BCA225 and CA15-3 are all recognized as members of the mucin family (15). This might be the reason why the serum levels of CA15-3, KL-6, and BCA225 are positively correlated with each other.

Since our investigation did not include any patients with advanced malignancies, we cannot discuss whether the

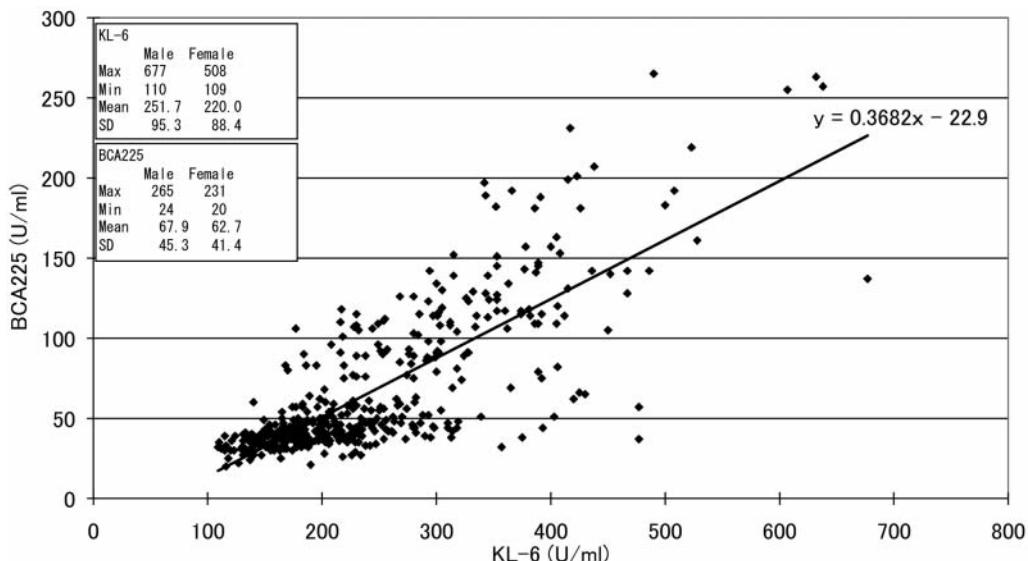


Figure 3. *KL-6 vs. BCA225 (correlation coefficient=0.79).*

combined use of these three tumor markers would actually improve the sensitivity and specificity of screening for malignancies. In our next study, we will further investigate the significance of these findings and the relationship of these markers in patients with advanced malignancies.

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