CA54/61 as a Marker for Epithelial Ovarian Cancer

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ABSTRACT

Using a new one-step, double-determinant enzyme immunoassay, we performed quantitative measurements of a mucin-type glycoprotein antigen (CA54/61) that we recently detected in sera of ovarian carcinoma patients. When the cutoff value was set at 12 units/ml, at which a high diagnostic efficiency was demonstrated (for at 20 units/ml [mean + 3 SD of healthy females]), the positive rates of ovarian serous, mucinous, clear cell, and endometrioid carcinomas were 76% (or 63%), 63% (or 55%), 57% (or 52%), and 50% (or 38%), respectively. Even in mucinous cystadenocarcinoma, more than one-half of the cases were positive, indicating the potential utility of the assay in the diagnosis of mucinous tumors. In sera from patients with benign ovarian tumors, only 9% (or 4%) of the cases were positive, indicating the quite high specificity of this test for ovarian carcinomas. To make a comparison between CA54/61 and CA125, we set the cutoff level of CA125 at 110 units/ml, at which 4% of the cases were positive, indicating the quite high specificity of this test for ovarian carcinomas. When the cutoff value was set at 12 units/ml, at which a high diagnostic efficiency was demonstrated (for at 35 units/ml [mean + 3 SD of healthy females]), when both CA54/61 and CA125 were assessed in sera from 36 patients with mucinous cystadenocarcinoma, the positive rates of CA54/61 and CA125 were 64% (or 56%) and 36% (or 56%), respectively, suggesting that CA54/61 is of clinical value as a new tumor marker for ovarian cancers, including mucinous tumors.

INTRODUCTION

CA125 (1, 2) is commonly used for the diagnosis of ovarian epithelial carcinomas, but low CA125 levels are frequently encountered in cases of mucinous cystadenocarcinoma. Even markers such as CA19-9 (3) and CEA4 (4, 5), which are often effective for the diagnosis of various kinds of adenocarcinomas, do not provide high positive rates in this type of ovarian tumor. Since mucinous tumors, along with serous tumors (including endometriotic cysts), are the most frequently encountered ovarian tumors, the development of markers useful for the diagnosis of mucinous tumors is an area of intense study. We have recently produced two monoclonal antibodies termed MA54 and MA61, both of which recognize the carbohydrate moiety in a high molecular weight mucin-type glycoprotein (6). Using these two antibodies, we developed a sandwich enzyme immunoassay for an antigen termed CA54/61 and found that the CA54/61 antigen was increased in the sera of patients with ovarian carcinomas including the mucinous type (6). In the present communication, using the improved assay system (6), we report the results of the CA54/61 assay of sera from patients with various ovarian lesions in a five-institution cooperative study and compare these results with those on CA125.

MATERIALS AND METHODS

Subjects. Sera were obtained from 348 healthy subjects, comprising 270 females and 78 males; from 351 patients with various noncancerous diseases, including 138 with ovarian benign tumors (including endometriotic cyst), 27 with ovarian borderline tumors, 122 with uterine myoma or adenomyosis, and 59 with benign disease of nongynecological organs: from 318 pregnant women; and from 43 umbilical cord veins. Also 9 samples of amniotic fluid were taken. In 11 females, samples were obtained at each stage of the menstrual cycle. Sera from 487 patients with various cancers, including 183 with ovarian cancers, 131 with uterine cervical cancers, 59 with uterine endometrial cancers, and 74 with cancers of nongynecological organs, were also assayed. A group of comparisons of different tumor markers was also performed, using a part of the samples mentioned above. In 138 patients with benign gynecological disease and 163 patients with ovarian cancer, CA54/61 and CA125 were measured simultaneously. In 85 and 27 patients with ovarian carcinoma, the simultaneous assay of CA54/61 and CA19-9 and that of CA54/61 and CEA were also performed, respectively.

Assay Systems. A new one-step, double-determinant enzyme immunoassay system (MKS-15) containing monoclonal antibody MA54 as the immobilized antibody on beads and MA61 as the horseradish peroxidase-labeled antibody was used. To the test tube were added a 30-μl serum sample, 250 μl of labeled antibody, and one bead coated with MA54. Incubation was carried out for 2 h at 37°C, followed by the enzyme reaction with 0.027% H2O2 and 3 mg/ml o-phenylenediamine in Macllvaine's buffer (48.5 mM citric acid-103 mM Na2HPO4, pH 5.0) as substrate and color developer, respectively. The absorbance was measured at 492 nm. When a 50-ng sample of the standard antigen, obtained from the void fractions of culture supernatants of human lung carcinoma cell line C1509 (6) by Ulgroel Aca 44 chromatography (IBF Bio-Technics, Villeneuve La Garenne, France), was defined as 1 unit of CA54/61, the measurable range of this assay was 1 to 200 units/ml. The coefficients of variation of intraassay (10 simultaneous measurements of 4 sera with the same assay kit) ranged from 2.5 to 7.5%, and the coefficient of variation of interassay (7 measurements of 4 sera with different assay kits) ranged from 4.4 to 6.5%. The recovery test was performed by the addition of 3 different concentrations of exogenous antigens to 3 sera, and the average of their recoveries was shown to be 91–102%. By serial dilutions of 3 sera, the concentration of CA54/61 decreased linearly with increasing dilutions, and the values obtained were those expected.

CA125 and CA19-9 were measured with radioimmunoassay kits (Centocor, Malvern, PA), and CEA was determined with an enzyme immunoassay kit (Roche, Basel, Switzerland).

RESULTS

CA54/61 Values in Healthy Subjects and in Pregnancy. The cutoff value of CA54/61 was set at two levels (Table 1). Since the mean value and the standard deviation for healthy females were 5.1 and 4.9 units/ml, respectively, the first cutoff level was set at 20 units/ml (mean + 3 SD of healthy females). The second cutoff level was set at 12 units/ml, at which a high diagnostic efficiency was obtained, as is shown later. Mean values for healthy females in various age groups and those at

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1 To whom requests for reprints should be addressed.

2 The abbreviation used is: CEA, carcinoembryonic antigen.
CA54/61 AS MARKER FOR EPITHELIAL OVARIAN CANCER

Table 1 CA54/61 values for healthy and for pregnant subjects

<table>
<thead>
<tr>
<th>Positive cases</th>
<th>Cutoff, 12 units/ml</th>
<th>Cutoff, 20 units/ml</th>
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<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Mean</td>
</tr>
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<tr>
<td>Female</td>
<td>270</td>
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</tr>
<tr>
<td>&lt;20 yr</td>
<td>21</td>
<td>5.9</td>
</tr>
<tr>
<td>20–29 yr</td>
<td>45</td>
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<td>30–39 yr</td>
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<td>50–59 yr</td>
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<td>5.4</td>
</tr>
<tr>
<td>&gt;70 yr</td>
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<tr>
<td>Pregnancy</td>
<td>318</td>
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</tr>
<tr>
<td>Umbilical vein</td>
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<tr>
<td>Amniotic fluid</td>
<td>9</td>
<td>41.7</td>
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Table 2 CA54/61 values for patients with various diseases

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<th>Cutoff, 12 units/ml</th>
<th>Cutoff, 20 units/ml</th>
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</thead>
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<tr>
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<td>Mean</td>
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<tr>
<td>Benign ovarian tumor</td>
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<tr>
<td>Serous cystadenoma</td>
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<tr>
<td>Mucinous cystadenoma</td>
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<td>3</td>
</tr>
<tr>
<td>Dermoid cyst</td>
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<td>2</td>
</tr>
<tr>
<td>Endometrioid cyst</td>
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<td>7</td>
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<tr>
<td>Others</td>
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<td>1</td>
</tr>
<tr>
<td>Ovarian borderline tumor</td>
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<td>3</td>
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<td>Ovarian carcinoma</td>
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<td>123</td>
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<td>Metastatic carcinoma</td>
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<tr>
<td>Uterus</td>
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<tr>
<td>Stomach (ulcer, etc.)</td>
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</tr>
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<td>Liver (hepatitis, etc.)</td>
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<tr>
<td>Others</td>
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<td>0</td>
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<td>Carcinoma</td>
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<td>Stomach</td>
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<td>Liver</td>
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<td>Colon</td>
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<td>3</td>
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<tr>
<td>Others</td>
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</table>

Fig. 1. Comparison of the diagnostic efficiency of CA54/61 and CA125. ○, sensitivity (S. E., proportion of patients with positive values among those with ovarian cancer); ●, specificity (S. P., proportion of patients with negative values among those with benign gynecological disease); △, false-positive rate (F. P., proportion of patients with positive values among those with benign gynecological disease); □, diagnostic efficiency (D. E., sensitivity x specificity).

Various stages of the menstrual cycle demonstrated no remarkable differences, and no definite trend was noted over the course of gestation in pregnant females. Forty-three umbilical blood samples yielded negative results; however, 78% (7 of 9) of the amniotic fluid samples gave higher values than the cutoff level of 20 units/ml, registering a relatively high mean value of 41.7 units/ml.

CA54/61 Values in Patients with Various Diseases. In patients with benign ovarian tumors [Table 2], the positive rate was 9% [13 of 138] at the cutoff level of 12 units/ml, [or 4% (6 of 138) at the cutoff level of 20 units/ml], and the patients with positive values included 3 [or 2] % with mucinous cystadenoma and 7, [or 4] % with benign endometrioid cyst. In borderline tumors, 11% [3 of 27] [or 7% (2 of 27)] of the patients had moderately high values, and 2 of them had mucinous tumors. Among patients with ovarian carcinoma, positive rates were 76% [55 of 72] [or 63% (45 of 72)] for serous cystadenocarcinoma, 63% [24 of 38] [or 55% (21 of 38)] for mucinous cystadenocarcinoma, 57% [13 of 23] [or 52% (12 of 23)] for clear cell carcinoma, 50% [8 of 16] [or 38% (6 of 16)] for endometrioid adenocarcinoma, 55% [6 of 11] for undifferentiated carcinoma, and 69% [9 of 13] [or 62% (8 of 13)] for metastatic carcinoma. Positive rates were less than 34% (or 23%), for patients with benign and malignant diseases aside from ovarian tumors.

Simultaneous Measurement of CA125 and CA54/61 in Patients with Gynecological Tumors. Simultaneous measurements of both CA125 and CA54/61 were performed on sera from 138 patients with benign gynecological diseases and 163 patients with ovarian carcinomas.

Fig. 1 indicates the sensitivity (proportion of patients with positive values among patients with ovarian carcinoma), the specificity (proportion of patients with negative values among patients with benign gynecological disease), the false-positive rate (proportion of patients with positive values among patients with benign gynecological disease), and the diagnostic efficiency (sensitivity x specificity) of CA54/61 and CA125 at various cutoff values. The sensitivity of both markers fell as the cutoff point was increased, with a complementary increase in the specificity. When the cutoff values were set at mean + 3 SD of healthy females (20 units/ml for CA54/61 and 35 units/ml for CA125), the sensitivity was 56 and 80%, the specificity was 96 and 61%, and the diagnostic efficiency was 0.54 and 0.49 for CA54/61 and CA125, respectively. In addition, another cutoff level of 12 units/ml for CA54/61 and 110 units/ml for CA125 was determined in order to compare both markers under the same situation where the sensitivity, specificity, false-positive rate, and diagnostic efficiency of CA54/61 were almost equal to those of CA125. CA125 and CA54/61 values and positive rates in sera of patients with gynecological benign and malignant tumors were compared using the two of cutoff levels mentioned above.

In benign gynecological diseases (Fig. 2), CA125 was positive in 40% [55 of 138] at the cutoff level of 35 units/ml [or 12% (17 of 138) at the cutoff level of 110 units/ml], and especially high positive rates, 64% [16 of 25] [or 24% (6 of 25)], were
CA54/61 and CEA was −0.04. Thus, no correlation was found between CA54/61 and either CA19-9 or CEA.

**DISCUSSION**

The clinical validity of tumor markers is evaluated by their sensitivity, specificity, and diagnostic efficiency. These values, however, change according to the cutoff value; thus it is important how the cutoff value is determined. The cutoff value should be set according to the clinical purpose.

In this study, CA54/61 was characterized as a new ovarian tumor marker demonstrating a low false-positive rate for healthy females (1.9%), healthy males (1.3%), and benign diseases (4.4%) and a high positive rate in ovarian carcinomas (57%) at the first cutoff level, which was calculated as the mean + 3 SD of healthy females. Currently, CA125 is being used widely as an ovarian tumor marker. It is well known, however, that CA125 measurements give a high false-positive rate for benign diseases, particularly endometriosis, and a high positive rate in ovarian carcinomas (66% for CA54/61 and 50% for CA125), so that abilities of CA125 and CA54/61 for picking up ovarian carcinomas were almost identical. Therefore, at these second cutoff levels, there was only a slight difference in positive rate for ovarian carcinomas (66% for CA54/61 and 65% for CA125) and in false-positive rate for gynecological benign diseases (11% for CA54/61 and 12% for CA125), as was shown in Fig. 1.

For comparison of the usefulness as an ovarian tumor marker between CA54/61 and CA125, simultaneous measurements were performed. The usefulness of a tumor marker is usually defined as the degree to which the marker discriminates between the malignant and benign diseases. This ability can be numeralyzed as the diagnostic efficiency which is calculated as the product of sensitivity × specificity. Since the maximum diagnostic efficiency spread over a wide range, as shown in Fig. 1, the diagnostic efficiency was attached one more condition where the false-positive rates in gynecological diseases were suppressed at about 10%. The second cutoff levels were thus determined at 12 units/ml for CA54/61 and 110 units/ml for CA125, so that abilities of CA125 and CA54/61 for picking up the ovarian carcinomas were almost identical. Therefore, at these second cutoff levels, there was only a slight difference in positive rate for ovarian carcinomas (66% for CA54/61 and 65% for CA125) and in false-positive rate for gynecological benign diseases (11% for CA54/61 and 12% for CA125), as was shown in Fig. 1. However, regarding these data, special attention should be paid to the fact that mucinous cystadenocarcinomas were significantly superior to CA125 in sensitivity for mucinous cystadenocarcinoma cases (P < 0.01).
Table 3  2 × 2 table analyses for simultaneous measurements of CA54/61 and CA125

A. First cutoff level (20 units/ml for CA54/61 and 35 units/ml for CA125)

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<thead>
<tr>
<th>CA54/61</th>
<th>Ovarian carcinoma (n = 163)</th>
<th>CA125</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>85 (52)a</td>
<td>7 (4)</td>
</tr>
<tr>
<td></td>
<td>(28)</td>
<td>131 (80)b</td>
</tr>
<tr>
<td></td>
<td>−</td>
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</tr>
<tr>
<td></td>
<td>46</td>
<td>25 (15)</td>
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<tr>
<td></td>
<td>(28)</td>
<td>71</td>
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<tr>
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</tr>
<tr>
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<tr>
<td></td>
<td>7 (19)</td>
</tr>
<tr>
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</tr>
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<td>52 (38)</td>
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<td>132</td>
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B. Second cutoff level (12 units/ml for CA54/61 and 110 units/ml for CA125)

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<td>121</td>
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<tr>
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*a Numbers in parentheses, percentage.
*b P < 0.001.
*c P < 0.01.
The combination assay of CA54/61 and CA125 at the second cutoff level is quite useful for reliable diagnosis of ovarian carcinomas. Also the combination assay of CA54/61 and another marker such as CA125, CA19–9, or CEA will be useful for the screening by the reason of their low correlation coefficients.

CA54/61 is a carbohydrate antigen recognized by two monoclonal antibodies, MA54 and MA61. The antigenic determinants reactive with these two antibodies differ; MA54 was found to recognize a mucin-type carbohydrate chain containing a terminal sialic acid (NeuAc α 2–6 galactose), whereas MA61 was shown to recognize a mucin-type carbohydrate chain without sialic acid (6). CA54/61, therefore, represents a molecule carrying these two antigenic determinants. Because many other different antigenic determinants are presumably present on this molecule, it may be possible to establish other assay systems utilizing antibodies that recognize different antigenic determinants on the CA54/61 molecule. Since mucin-related markers such as CA72–4 have also been reported (10), comparisons with these tumor markers will require attention in the near future.

We have demonstrated that CA54/61 in itself is a useful tumor marker for ovarian cancers, characterized by low positive rates for other carcinomas and benign diseases and the high positive rate for ovarian cancers including mucinous cystadenocarcinoma. It has been documented, on the other hand, that CA125 is a useful ovarian tumor marker because of the very high positive rate for ovarian cancers, even though it also shows high false-positive rates for benign diseases, especially for endometriosis (8), when the cutoff value is set at the mean + 3 SD (35 units/ml) of healthy females. Taking all of these data together, we foresee that CA54/61 will be of clinical value as a new tumor marker to supplement some of the disadvantages of CA125 in view of its considerably low false-positive rate and favorable sensitivity for mucinous cystadenocarcinoma.

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CA54/61 as a Marker for Epithelial Ovarian Cancer

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