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Tumour associated antigen CA-50, CA-242 immunoradiometric assay (IRMA) in genitourinary malignancy and gastrointestinal carcinoma early diagnosis

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Title of Project Tumor Associated Antigen CA-50, CA-242 Immunoradiometric Assay (IRMA) in Genitourinary Malignancy and Gastrointestinal Carcinoma Early Diagnosis

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Period of Contract May 15, 1991 - May 14, 1992

Summary:

Having introduced C-50, C-242 monoclonal antibodies from Professor Leif Lindholm, Pharmacia CanAg, Sweden, we developed the immunoradiometric assay of CA-50 in 1988 [1] and immunoradiometric assay of CA-242 in 1991 [2], and applyed these assays widespreadly in clinical diagnostic research of many kinds of carcinomas [3].

Using the immunoradiometric assays (IRMA) of serum CA-50 and CA-242, we have detected 1183 cancer patients including colo-rect Ca 263, pancreas and cholecyst Ca 200, liver Ca 167, stomach Ca 208, genitourinary Ca 120, and other cancers 225; normal individuals 145, benign diseases 289. The normal values were 6.38±6.64u/ml(N=68) for CA-50, and 2.5±4.5u/ml (N=77) for CA-242. >20u/ml for CA-50 and >12u/ml for CA-242 were taken as positive.

The serum CA-50 were 53.56±58.96u/ml for 734 cancer patients and 8.53±8.41 u/ml for 108 cases of benign diseases with significant difference between the two groups (P<0.001). The mean positive rate for several kinds of cancer patients was 65.64%,showing very high detective rate of 96.6% for pancreas and cholecyst carcinomas, relatively high positive rates for colorectum Ca 64.1%, liver Ca 76.5%, genitourinary Ca 64.6%, and lung Ca 66.6%, and the low one for breast and esophageal cancers.

The serum CA-242 were 52.19±66.95u/ml for cancer patients and 3.5±4.69u/ml for benign diseases (N=449 and N=181 respectively), indicating significant differences between the malignant and benign groups (P<0.001). The positive detective rates were 67.41% for 449 patients with different carcinomas, and 88.1% for 109 cases of pancreatic and cholecyst carcinomas. The positive rates for other cancers from ovary, uterus, lung, head and neck, and genitourinary system were 70.8% (N=24, Ov. & Ut.), 76.9% (N=13, lung), 86.6% (N=15,head & neck), and 75% (N=12, Genit.), respectively.

Comparing the CA-242 and CA-50, the CA-242 was better than CA-50 in detection of breast cancer, but the CA-50 was better than CA-242 in diagnosis of liver cancer.

The ROC (Receiver-operating characteristic curves) analyses were made for CA-50 and CA-242 assays with respect to the sensitivities and the specificities for series of different carcinomas.

The significant feature of CA-242 and CA-50 immunoradiometric assays was the high detective rates for pancreatic and cholecyst carcinomas.

The results of CA-50 and CA-242 detections for different malignant and benign diseases were summarized in table 1.

Table 1. CA-50 and CA-242 Serum Levels in different Malignant and Benign Diseases

Carcinoma and Benign Diseases	CA-50 (u/ml)			CA-242(u/ml)		
	N	X±SD	POsitivity%	N	X±SD	Positivity%
Colo-rect Ca	145	39.92±45.60	64.1	118	52.92±76.62	63.36
Benign	14	2.68±3.23	0	27	2.00±3.08	0
Pancrease, Chole-cyst Ca	91	124.84±121.85	96.6	109	84.17±79.90	88.1
Benign	14	21.50±26.75	28.5	38	4.74±6.78	13.1
Liver Ca	83	78.19±81.50	76.5	84	29.15±40.45	49.9
Benign	33	5.69±4.31	0	69	3.72±5.51	11.5
Lung Ca	59	39.97±46.71	66.6	13	48.1±56.41	76.9
Benign	9	7.00±4.00	0	6	2.45±2.27	0
Stomach Ca	145	41.16±36.36	51	63	40.95±83.44	49.2
Benign	10	8.07±9.80	10	18	2.59±2.80	0
Ovarian, Uterus Ca	47	46.34±81.01	60.5	24	33.42±36.65	70.8
Benign	5	10.7±6.78	20	4	3.00±2.45	0
Beast Ca	26	21.37±24.18	38.5	15	32.57±42.17	60
Benign	8	5.52±2.66	0	6	1.50±1.52	0
Head, Neck Ca	19	28.95±28.67	57.9	15	33.98±17.91	86.6
Benign	6	5.61±5.51	0	5	5.96±1.73	0
Genitourinary Ca	108	34.76±42.00	64.6	12	42.98±81.24	75
Benign	9	13.06±13.78	11.1	8	3.93±4.70	0
Esophageal Ca	11	28.14±32.1	45.5	6	7.65±10.45	16.6
Total Malignant	734	53.56±58.94	65.64	449	52.19±66.95	67.41
Total Benign	108	8.53±8.41	6.47	181	3.50±4.69	7.13
Normals	68	6.38±6.64	4.7	77	2.5±4.5	4.0

It is concluded that CA-50 and CA-242 IRMAs are very useful indicators for cancer diagnoses and for differential diagnoses of malignant diseases from benign ones. Their false positivity among normal individuals is below 4.7%.

The papers published:

1. Immunoradiometric assay for tumor associated antigen CA-50, Acta Academiae Medicinae Sinicae, 10(4):2(2, 1988
2. Immunoradiometric assay for carbohydrate antigen CA-242, Chinese Journal of Nuclear Medicine, 11(4):241, 1991
3. Establishment and applications of immunoradiometric assays for several tumor markers, Journal of Monoclonal Antibody, 7(3):54, 1991

Scientific Background and Scope of project:

In 1980s accompanied with progress of monoclonal technique, many new radioimmunoassays for cancer diagnoses were developed. Taking tumor cell lines, tumor extractions as antigens and based on hybridoma techniques, a great deal of tumor specific monoclonal antibodies were prepared. These McAbs were widely used in radioimmuno-serological, immunohistochemical and radioimaging detections of carcinomas. Among these new methods the carbohydrate antigens CA-19-9, CA-125, CA-50, and CA-242 radioimmuno-serological assays are most valuable indicators in cancer diagnoses and monitoring. Recently we introduced C-50 and C242 McAbs from Professor Leif Lindholm, Sweden, developed CA-50 IRMA and CA-242 IRMA, and widely applied these assays to diagnoses and monitoring of several kinds of carcinomas. The results of this research are reported as follows.

Experimental Method:

1. Materials and reagents: McAbs C-50, C-242, standards CA-50 and CA-242 were from Pharmacia CanAg, Sweden; Iodogen was gift of Dr. Prasad, India; Bovin serum albumin(BSA), NaN_3, Tween 20, Sigma USA.

Clinical samples: Normal sera were from blood donors of blood bank. Serum samples of malignant and benign diseases were taken from out-,and in-patients at Cancer Hospital, CAMS, and stored in -20 C till test. All diagnoses were confirmed by pathology.

2. CA-50 test: The serum CA-50 contents were detected by CA-50 IRMA established by us in 1988[1].

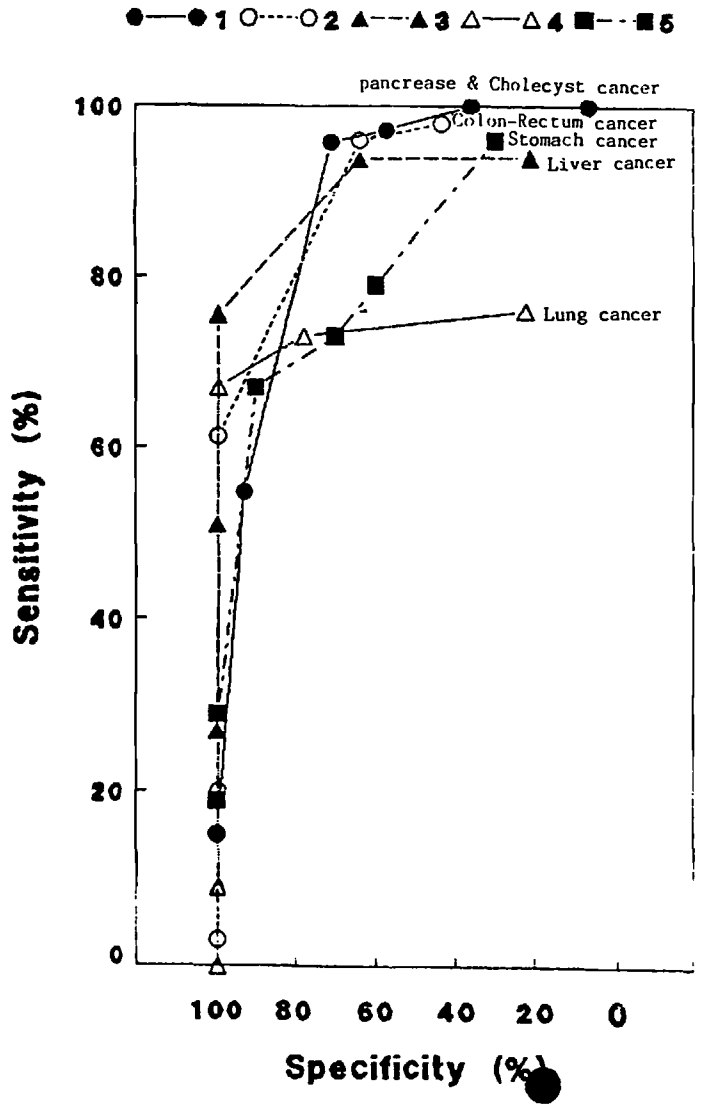
3. CA-242 test: The CA-242 contents in the sera were detected by CA-242 IRMA established by us in 1991 [2]. 50ul of CA-242 standards in series of amounts 0, 10, 20, 40, 80, 160 u/ml or 50 ul of sera for nuknown sample test tubes were added into the tubes, followed by adding 150 ul assay buffer and 1 McAb coated bead into each tube for the Ab-Ag reaction at room temperature for 1.5-3 h with stirring. The liquid was removed from the tubes and the beads were washed with washing buffer two times. Then, 200 ul of 125-I-labelled C-242 McAb were added to have another Ab-Ag reaction at room temperature for 1-2 h (or overnight at 4 C). The reaction mixture was removed, the beads were washed 3 times with ditilled water, and then counted for the radioactivity to give the standard curve and to determine the CA-242 amounts in u/ml in the unknown serum samples.

Results obtained:

1. The results of detection of serum CA-50 and CA-242 among 1183 cancer patients, 289 cases of benign diseases, and 145 normal individuals were shown in table 1 (see summary). There are significant differences of CA-50 and CA-242 values with respect to malignant VS normals and malignant VS benign diseases; but there is no significant difference between benign diseases and normal individuals. Both CA-50 and CA-242 have most satisfactory positive detective rates of 96.6% CA-50 and 88.1% CA-242 for pancreatic and chole-cyst cancers with relatively a bit higher false positive detective rates of 28.5% CA-50 and 13.1% CA-242. Ca-50 and CA-242 are also useful indicators for several other carcinomas with different positivities. Ca-242 shows higher positivities for ovarian, uterus, breast, lung, head & neck and genitourinary carcinomas than that of CA-50, but CA-50 is better for liver cancer detection. Combined detection of CA-50 and CA-242 will raise the accuracy of carcinoma diagnoses.

2. ROC (Receiver-Operating Characteristic) Curve and sensitivity, specificity, and accuracy of cacer diagnoses: Sensitivities, specificities of CA-50 and CA-242 IRMAs at series of different cut-off values for 9 kinds of carcinomas were shown in fig 1 and fig 2. It can be seen that the best curves are for pancreatic and chole-cyst cancers with very high sensitivity and specificity of diagnoses either in CA-50 IRMA or in CA-242 IRMA. The sensitivities, specificities, and accuracies of cancer diagnoses at cut-off values 20u/ml CA-50, 12u/ml CA-242 were shown in table 2. It was concluded that among 9 kinds of cancers, apart from ovarian, uterus, and breast cancers in CA-50 IRMA, and liver and stomach cancers in CA-242 IRMA,many other carcinomas could obtained relatively high sensitivity, specificity and accuracy of diagnoses.

Fig 1.


CA-50 IRMA ROC CURVE (1)
1 2 3 4 5
pancrease & Cholecyst cancer
Colon-Rectum cancer
Stomach cancer
Liver cancer
Lung cancer
Sensitivity (%)
Specificity (%)
100
80
60
40
20
0

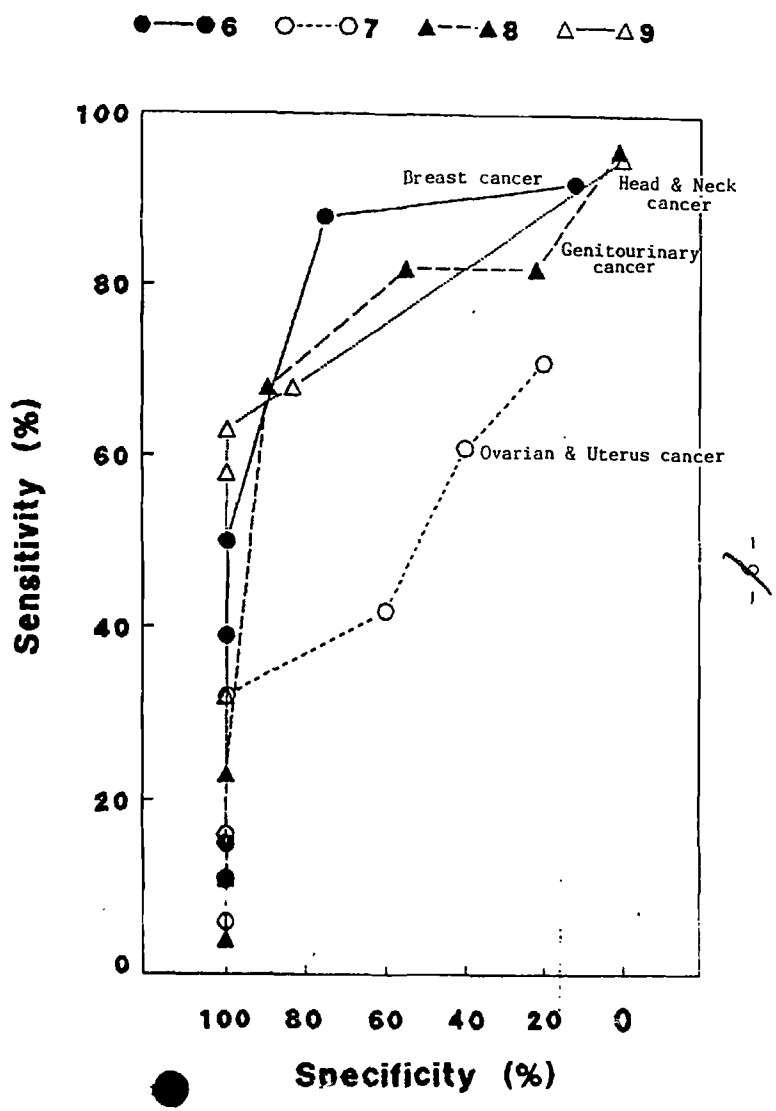
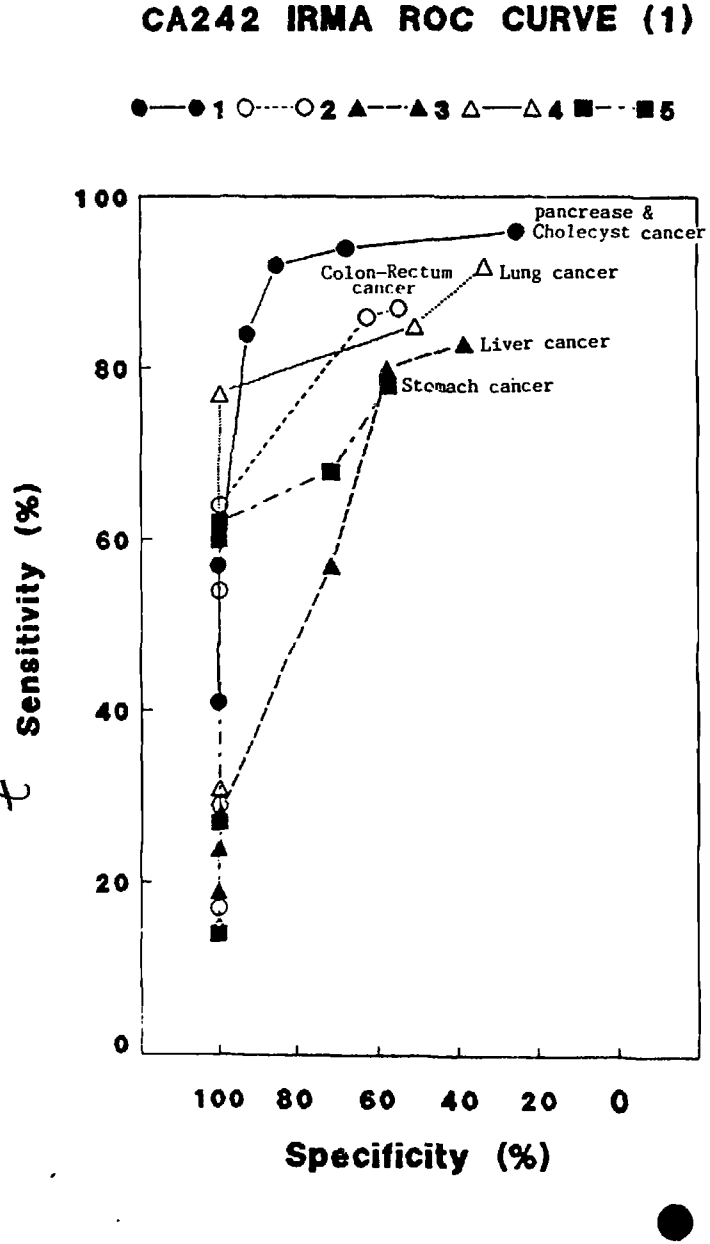

CA-50 IRMA ROC CURVE (2)
6 7 8 9
Breast cancer
Head & Neck cancer
Genitourinary cancer
Ovarian & Uterus cancer
Sensitivity (%)
Specificity (%)
100
80
60
40
20
0

Fig 2.


CA242 IRMA ROC CURVE (1)
1 2 3 4 5
pancrease & Cholecyst cancer
Colon-Rectum cancer
Lung cancer
Liver cancer
Stomach cancer
Sensitivity (%)
Specificity (%)
100
80
60
40
20
0

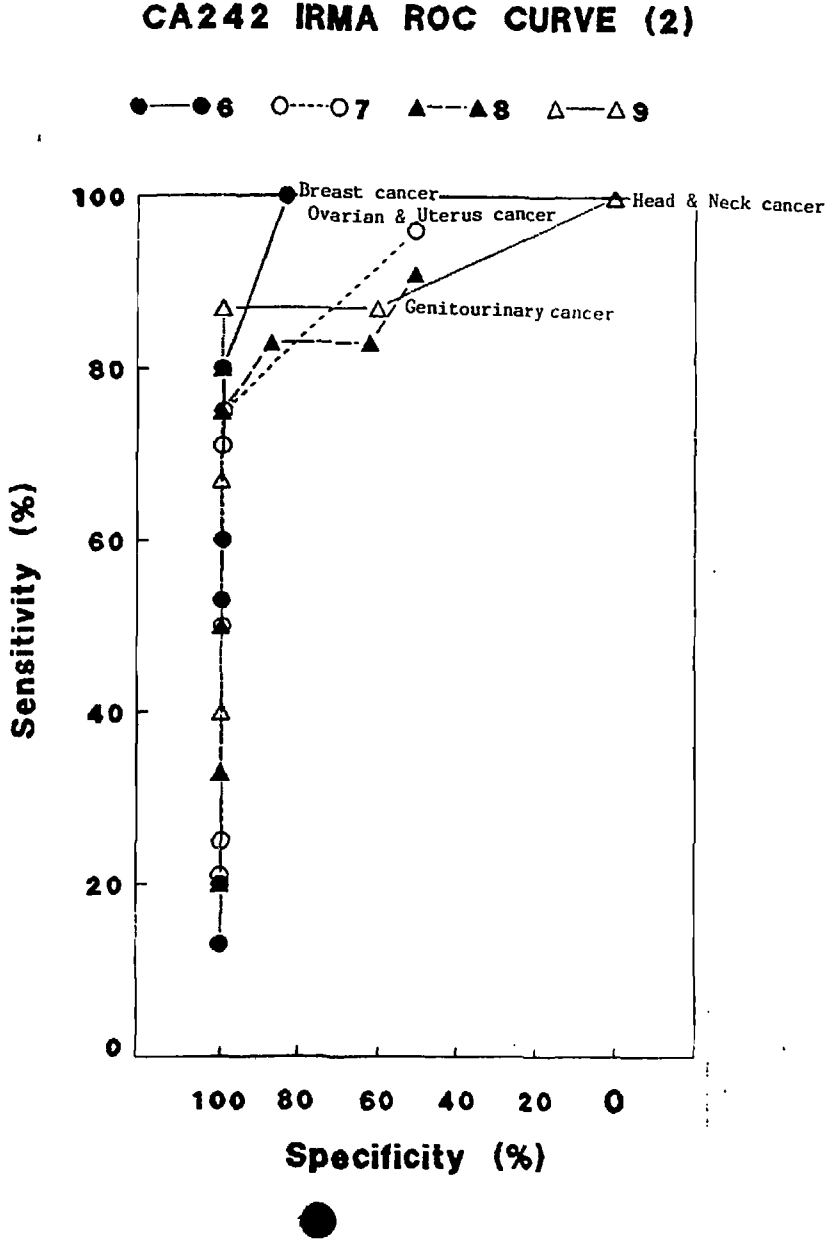

CA242 IRMA ROC CURVE (2)
6 7 8 9
Breast cancer
Ovarian & Uterus cancer
Head & Neck cancer
Genitourinary cancer
Sensitivity (%)
Specificity (%)
100
80
60
40
20
0

Table 2. Sensitivity, Specificity, and Accuracy of CA-50 and CA-242 for Different Carcinomas

Carcinomas	CA-50(Positive>20u/ml)			CA-242(Positive>12u/ml)		
	Sensitivity %	Specificity %	Accuracy %	Sensitivity %	Specificity %	Accuracy %
Pancreas,Cholecyst Ca	96.6	71.5	84.05	88.1	86.9	87.5
Colo-rect Ca	64.1	100	82.05	63.36	100	81.88
Liver Ca	76.5	100	88.25	49.9	88.5	69.2
Stomach Ca	51.0	90	70.5	49.2	100	74.6
Lung Ca	66.6	100	83.3	76.9	100	88.5
Ovarian, Uterus Ca	60.5	80	73.3	70.8	100	85.4
Breast Ca	38.5	100	69.3	60.0	100	80.0
Genitourinary Ca	64.6	88.9	76.8	75.0	100	87.5
Head, Neck Ca	57.9	100	78.9	86.6	100	93.3
Total	65.64	93.53	79.6	67.53	92.87	80.2

Conclusions:

The results of CA-50 and CA-242 detection for 1183 cancer patients in 9 kinds of different carcinomas showed:

1. Ca-50 and CA-242 are the best diagnostic indicators for pancreatic and cholecyst cancers.

2. The diagnostic positivity order for CA-50 is : pancreatic-cholecyst, liver, lung, genitourinary, colo-rect, ovarian-uterus, head-neck, stomach, breast cancers.

3. The diagnostic positivity order for CA-242 is: pancreatic-cholecyst, head-neck, lung, genitourinary, ovarian-uterus, colo-rect, breast, liver, stomach cancers.

4. CA-50 and CA-242 IRMAs can be used in differentiation between malignant and benign diseases.

5. CA-50 and CA-242 can be used in monitoring of cancer therapy and cancer recurrence (see also the progress report of last year).

6. Combined detection of CA-50 and CA-242 could improve sensitivity and specificity of cancer diagnoses, and combined detection of CA-50 and alpha-fetoprotein could further raise the positivity of liver cancer diagnosis.

Papers Published on Work Done Under the Contract:

The papers published are listed after the Summary of this report.