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Perspectives in Cancer Research

Tumor Markers in Non-Malignant Diseases

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Abstract—*This paper reviews the specificity of tumor markers recently introduced in clinical use, namely CA 19-9, CA 125, CA 15-3, CA 50 and SCC antigen. It appears that a large number of either biological conditions (age, sex, pregnancy, menstruation etc.), intoxication (smoking and alcohol addictions) or various non-malignant diseases do affect the serum levels of tumor markers. These data are of practical use in the interpretation of tumor marker determinations in the follow-up of cancer patients.*

INTRODUCTION

TUMOR MARKERS (especially oncofetal or tumor associated antigens, hormones and enzymes) have been documented in a large number of cancers. They have been used clinically to aid in differential diagnosis, to give an index of stage of disease and to provide an index of response to therapy and tumor recurrence [1]. Because of the increasing demands for their determinations, their effectiveness has often been exaggerated. The specificity of tumor markers in general is poor. Indeed, a large number of non cancer diseases give false positive results [2]. Therefore, we found it worthwhile to document the effects of biological factors (age, sex, pregnancy, etc.) intoxication (smoking and alcohol habits) and non-malignant diseases on serum levels of carbohydrate antigens recently introduced into the clinic namely CA 19-9, CA 125, CA 15-3, CA 50 and TA-4 and its subfraction SCC antigen.

CA 19-9

CA 19-9 is a carbohydrate antigenic determinant which has been identified as a sialylated lacto-*N*-fucopentaose II, an oligosaccharide sharing structural features with Lewis blood group substances [3, 4]. It has been found on glycoproteins in the sera of cancer patients [5], more specifically in those with colorectal, gastric and pancreatic cancer [6, 7].

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1. *Biological factors*

On a large series of 2700 healthy blood bank donors, 0.4% had levels of the marker higher than 37 U/ml which is considered a cut-off value [8]. Their serum mean level was 8.4 ± 7.4 U/ml [8]. A sex difference was reported with slightly higher levels in females [9]. In addition, the mean concentration of serum CA 19-9 did vary with age in healthy females: values were highest in the 20–29 year-old group and lowest between 60 and 69 years of age, these variations being of relatively low amplitude [10]. However, these findings could well be due to the incidence of menstruation in young females, which is known to increase the serum values of some markers [11]. With respect to pregnancy CA 19-9 levels were found higher than 37 U/ml in 4.8% of 21 pregnant women (trimesters of pregnancy not specified). Last, smoking addiction results in only slight alterations in the mean level of the marker [9]. Literature data are displayed in Table 1.

2. *Non-malignant diseases*

CA 19-9 is increased in a large set of benign diseases. About 20% of patients with miscellaneous liver diseases including cirrhosis and cholelithiasis have serum values of CA 19-9 over 37 U/ml. The data reported in patients with hepatitis are inconclusive since they range from about 2 to 23% of positivity [12, 13]. CA 19-9 determination is considered a sensitive test for pancreatic cancer. Nevertheless, patients with acute or chronic pancreatitis may have elevated serum levels, with the

Table 1. *CA* 19-9 *in healthy males and females*

		References	No. of subjects	Percentage of subjects with level >37 U/ml	Mean ± S.D.
Healthy controls	Both sexes	[8]	2700	0.4	
	Both sexes	[36]	310	3.5	
	Both sexes	[37]	40	0.0	
	Both sexes	[14]	31	0.0	
	Both sexes	[9]	496	1.6	10.5 ± 9.4
	Females		208		11.9 ± 9.9
	Males		288		9.5 ± 9.0
	Both sexes	[12]	222		11.2 ± 10.4
	Females		98		14.4 ± 14.2
	Males		127		8.5 ± 4.3
Smokers	Both sexes	[8]	59	1.7	
	Females: yes	[9]	93		11.3 ± 8.5
	no		115		12.5 ± 10.9
	Males: yes		121		10.2 ± 9.8
	no		167		8.9 ± 8.3
Pregnancy	All trimesters	[12]	21	4.8	

percentage of false positives varying from 3 to 30% depending on the authors [14, 15]. Last, a relatively small percentage (most often less than 10%) of patients with increased serum CA 19-9 levels has been reported in various benign diseases (Table 2). A noticeable variability in the percentage of patients with elevated CA 19-9 levels is observed for a pathology determined in different studies dealing with hepatitis, cholelithiasis and chronic renal failure (Table 2). However, it is difficult to compare the different populations studied since a number of factors which are known to modify the level of the marker are not taken into account from one study to another, e.g. smoking addition and stage of the diseases, among others.

CA 125

CA 125 is a carbohydrate antigen determinant associated with a high molecular weight glycoprotein that is expressed in some derivatives of celomic epithelium [16]. It has been used primarily in the detection and investigation of patients with non-mucinous ovarian cancer [17]. Elevated serum levels were also found in patients with carcinoma of the endometrium, Fallopian tube and breast [16, 18, 19].

1. *Biological factors*

In a series of 888 apparently healthy persons, Bast *et al.* [20] showed that 1% had levels exceeding the cut-off value of 35 U/ml. The mean level was 8.7 ± 8.9 U/ml [20]. A sex-difference in the level of the marker was found by Klug *et al.* with values slightly higher in females (Table 3). A slight dependence of serum CA 125 levels on age with a trend to decrease with increasing age has also been reported [21]. In contrast, such age and sex-differences were not found by Green *et al.* [9]. Trends towards slightly decreased mean serum levels of CA 125 among smokers were of borderline significance [9, 22].

2. *CA* 125 *levels in pregnancy, menstruation and gynecologic disorders*

Significant serum elevation of the marker was observed in the first trimester of pregnancy in comparison with values in the second or third trimester [18, 22]. This elevation may result from hyperproduction of CA 125-associated glycoprotein by the fetus and subsequent transfer to mother. From the data reported by Nilof *et al.* [18] it can be assumed that about 50% of females in the first trimester of pregnancy have CA 125 levels over 35 U/ml and 16% over 65 U/ml.

Serum CA 125 concentrations can fluctuate markedly during the menstrual cycle. Levels higher than 35 U/ml are found in about 30% of the menstruating females studied [11]. In one case recently reported, within 1 day after the onset of the menstrual period, the serum CA 125 concentration increased by 10–20-fold. Values subsequently decreased steadily during the remainder of the cycle [24]. It has recently been demonstrated that endometriosis is often accompanied with high levels of CA 125 [11, 25, 26]. The levels were found to correlate with the severity of endometriosis. About 10% of patients with stage I–II and 40% of patients with stage III–IV endometroisis had levels higher than 35 U/ml (Table 4).

Table 2. Positivity of Ca 19–9 in patients with benign diseases

		References	No. of patients	Percentage of patients with level >37 U/ml
Cirrhosis		[8]	106	19.0
		[12]	78	16.7
		[13]	36	19.4
Hepatitis		[8]	103	3.9
		[12]	76	2.6
		[13]	52	23.0
		[36]	31	22.5
Cholelithiasis		[13]	45	44.0
		[36]	40	27.0
		[12]	24	16.0
		[37]	6	16.6
Miscellaneous liver diseases		[36]	64	21.8
		[38]	27	15.0
Pancreatitis	Acute	[13]	84	22.0
		[39]	36	11.0
		[15]	13	30.7
	Chronic	[39]	66	27.0
		[13]	38	21.0
		[40]	30	6.6
		[14]	29	3.4
		[37]	22	4.5
	Acute and chronic	[8]	34	2.9
		[38]	32	16.0
		[12]	24	8.3
		[41]	21	4.8
Chronic renal failure		[12]	42	4.8
		[36]	18	0.0
Peritonitis		[13]	26	11.5
Respiratory diseases		[13]	68	2.9
		[36]	38	5.3
Autoimmune diseases		[8]	100	2.0
		[13]	59	3.3
		[36]	38	0.0
		[42]	8	0.0
G.I. diseases				
	Miscellaneous	[42]	51	0.0
	Miscellaneous	[13]	18	5.5
	Duodenal ulcer	[36]	47	4.3
	Peptic ulcer	[36]	23	0.0
Diabetes		[12]	78	16.7
Endocrine diseases		[13]	115	6.0
		[42]	18	0.0
		[36]	12	9.0

A various percentage (5–29%) of females with pelvic inflammation diseases had elevated levels of the marker. Last, a small percentage of elevated level has been reported in females suffering from miscellaneous benign gynecologic diseases (Table 4).

Table 3. CA 125 in healthy males and females

		References	No. of subjects	Percentage of subjects with level >35 U/ml	Mean ± S.D.
Healthy controls	Both sexes	[20]	888	1.0	8.7 ± 8.9
	Females		351	1.4	7.9 ± 8.0*
	Males		537	0.7	8.0 ± 9.4
	Both sexes	[9]	496	0.8	9.0 ± 8.0
	Females		208		10.3 ± 11.3
	Males		288		8.0 ± 5.3
	Both sexes	[21]	56	0.0	11.2 ± 5.4
	Females		26	0.0	13.1 ± 6.8*
	Males		30	0.0	9.7 ± 3.2
	Both sexes	[43]	226	1.8	0.9 ± 11.0
Smokers	Males: yes	[9]	121		7.4 ± 4.3
	no		167		8.4 ± 5.9
	Females: yes		93		8.4 ± 5.3
	no		115		11.8 ± 15.1
	Males: yes	[22]	25		7.2 ± 5.7
	no		25		6.6 ± 4.1

*A sex-difference was validated (ANOVA).

3. *CA 125 levels in benign non-gynecologic diseases*

A number of papers have focused on the effects of non-malignant liver and biliary diseases on CA 125 levels (Table 5). Fifty per cent of patients with cirrhosis had elevated levels of the marker [27]. The point to underline is that elevated levels were observed in all patients with ascites. Thus, CA 125 is a non-specific marker of ascite whatever its origin: ovarian carcinoma, cirrhosis, peritoneal inflammatory process, hepatocellular carcinoma etc. [27]. In addition, CA 125 levels were always found higher in the ascitic fluid than in the serum. Therefore, CA 125 might be of interest for assessing the presence of clinically undetected peritoneal inflammatory process or in patients with chronic liver diseases. About 10% of patients with acute or chronic hepatitis had increased levels (Table 5). Conflicting results have been reported on the frequency of elevated levels in patients with acute pancreatitis and respiratory diseases (Table 5). Since the number of subjects studied was small (n = 5–20) and the stage of the disease was not documented, these data would need further assessment.

CA 15-3

CA 15-3 is a carbohydrate antigen associated with a high molecular weight (290 kD) glycoprotein, defined by two monoclonal antibodies (115D 8 and DF 3). The main use of the marker is the follow up of patients suffering from breast cancer especially in patients with metastatic carcinoma [28–31].

Few data are available on this marker (Table 6). In a large series of 1050 healthy controls, Hayes *et al.* [29] found that 1.3% subjects had values exceeding the chosen cut-off value (30 U/ml). The mean level was 13.3 ± 6.0 U/ml [29]. No sex or age difference could be validated [30]. Levels over 30 U/ml could not be observed in lactating or pregnant women [29]. The main false positive rates occurred in benign liver diseases (Table 6).

CA 50

CA 50 is a carbohydrate antigen which occurs as a ganglioside and as a sialylated glycoprotein [32]. This marker has been found in various types of carcinomas [33]. In healthy controls, less than 1% of subject had values over 25 U/ml, a figure considered as a cut-off value [34]. Few papers are available on this marker [34, 35]. Among the benign diseases studied, only cirrhosis and pancreatitis markedly increased the incidence of positivity of this marker (Table 7).

TUMOR-ASSOCIATED ANTIGEN TA-4 AND SCC

TA-4, a tumor-associated antigen, is a glycoprotein with a molecular weight of 48 kD [47] found in elevated concentrations in blood of patients with squamous cell carcinoma of the uterine cervix

[47, 48]. TA-4 and its subfraction, the SCC tumor marker antigen, were also found to be elevated in some patients with other cases of squamous cell carcinoma, e.g. lung, pharynx, larynx, tongue, palate, neck and lung cancers [47, 48]. Based upon the mean value in healthy subjects plus two standard deviations, a serum TA-4 value of 2.5 ng/ml was arbitrarily taken as the upper limit of normal; in these conditions two of 36 healthy subjects (5.5%) had serum TA-4 values slightly higher than the arbitrary norm [49]. Few data are available on this marker (Table 8).

CONCLUSION

Thus, it appears that a large number of benign diseases can increase the serum levels of tumor markers. However, further investigations needed to clarify the discrepancy observed in the frequency of elevated serum levels of some markers (CA 19-9, CA 125) in benign conditions should take into account the possible part played in by some parameters known to modify the values of tumor markers, e.g. smoking or alcohol addiction, age and sex, stage of the studied diseases. In any case, all these biological and non-malignant pathological factors which have been shown to give false positive results are of practical use and must be kept in mind to avoid a misinterpretation in the tests used for the follow-up of cancer patients.

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Table 4. Positivity of CA 125 in pregnancy, menstruation and benign gynecologic diseases

		References	No. of females	Percentage of females with level >35 U/ml	Mean ± S.D.
Trimester of pregnancy	First	[18]	38	55.0	
	Not defined	[44]	46	24.0	
	Not defined	[11]	15	20.0	25.8 ± 19.8
	First	[22]	29		85 ± 101
	Second		21		20 ± 10
	Third		21		25 ± 27
Menstruation		[11]	21		34.5
Endometriosis					
	Stage I	[11]	55	1.8	13.6 ± 6.8
	Stage II		37	13.5	22.8 ± 15.5
	Stage III		30	30.0	27.8 ± 17.3
	Stage IV		8	50.0	43.6 ± 28.0
	Stage I/II	[26]	22	9.0	19.9 ± 9.2
	Stage III/IV		15	20.0	28.5 ± 23.6
	Stage I	[25]	23	0.0	
	Stage II		24	13.0	
	Stage III/IV		13	54.0	
Pelvic inflammatory diseases		[25]	21	5.0	
		[11]	7	28.6	
		[44]	30	17.0	
		[18]	21	9.5*	
Miscellaneous	Vaginitis/cervitis	[18]	87	0.0*	
	Ovarian cyst		25	0.0*	
	Adenomyosis	[25]	4	0.0	
	Leiomyomata uteri		7	14.0	
	Leiomyomas	[18]	45	4.4*	
	Miscellaneous†		988	1.1*	
	Normal annual check up		652	0.2*	

*The cut off value was 65 U/ml.

†Patients not defined attending the gynecologic clinic (pregnant women excluded).

Table 5. Positivity of CA 125 in non-gynecologic benign diseases

		References	No. of subjects	Percentage of subjects with level >35 U /ml
Cirrhosis		[23]	17	35.0
		[45]	14	86.0
	With ascitis	[27]	15	100.0
	Without ascitis		16	50.0
	Icteric	[46]	9	88.0
	Non icteric		14	43.0
	Non cirrhotic icteric		24	29.0
Hepatitis	Acute	[43]	16	12.5
	Chronic		23	7.7
	Chronic active	[23]	20	10.0
Cholelithiasis		[23]	14	0.0
Chronic renal failure		[43]	29	10.3
		[44]	50	8.0
Pancreatitis	Acute	[43]	13	61.5
		[23]	5	0.0
	Chronic	[23]	46	0.0
Respiratory diseases		[43]	20	20.0
		[45]	5	0.0
Autoimmune diseases		[43]	223	13.0
Peritonitis		[43]	12	75.0
Diabetes		[44]	10	0.0
Endocrine diseases		[43]	36	8.3

Table 6. CA 15-3 in health and benign diseases

		References	No. of subjects	Percentage of subjects with level >30 U/ml	Mean level ± S.D.
Healthy controls	Both sexes	[28]	1051	1.0	
	Females	[29]	1050	1.3	13.3 ± 6.0
	Females	[30]	81	0.0	13.8 ± 3.9
	Males		26	0.0	15.1 ± 5.0
Smokers		[28]	500	0.0	
Pregnancy		[29]	20	0.0	12.6 ± 4.0
Lactation		[29]	16	0.0	13.0 ± 4.0
Breast diseases	Fibrocystic diseases	[30]	18	5.5	18.8 ± 7.5
	Fibroadenoma		21	0.0	14.5 ± 5.9
	Miscellaneous	[29]	25	8.0	16.5 ± 9.0
Liver diseases	Acute hepatitis	[29]	8	38.0	24.7 ± 10.0
	Chronic active heptatitis		7	29.0	25.4 ± 13.0
	Cirrhosis		26	31.0	26.8 ± 19.0
	Miscellaneous		11	27.0	25.1 ± 16.0
	Miscellaneous	[30]	48	25.0	25.4 ± 9.4

Table 7. CA 50 in health and benign diseases

	References	No. of subjects	Percentage of subjects with level >25 U/ml
Healthy controls	34	150	0.6
	35	293	4.0
Smokers	35	141	3.5
Cirrhosis	35	33	60.6
Pancreatitis	35	18	38.9
Ulcerative colitis	35	120	6.6
	34	28	7.0
Pneumonia	34	42	0.0

Table 8. TA-4 in health and benign diseases

	References	No. of subjects	Percentage of subjects with abnormal levels	Mean level ± S.D. (ng/ml)
Healthy females	[47]	20	0*	
	[49]	36	5.5	1.3 ± 0.6
	[50]	102	0*	
Pregnancy	[47]	10	0*	
Benign gynecologic diseases	[49]	10	0*	1.8 ± 0.7
	[50]	77	0*	

*Levels were first expressed as arbitrary units (<5 μU/ml).

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