Menstrual cycle values of tumor marker in healthy women and in patients with non-gynecological tumors

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Summary: The aim of the present study is to investigate whether the values of CA 12-5 which is considered a specific ovarian tumor marker can be used in patients with non-gynecological tumors whose values in menstrual cycle phases were not previously investigated. In order to determine whether a particular phase or a combination of phase are important, CA 12-5 values were determined by radioimmunoassay technique in a limited number of patients belonging to three different age groups. CA 12-5 were found to be unrelated to age. No statistically significant difference in CA 12-5 values was noted between samples obtained from patients with tumor and healthy women on the first and second days of menstruation. In both cases the normal value exceeded 35 U/ml. The mean values was 42 U/ml in healthy women and 49 U/ml in tumor patients. Mean CA 12-5 values determined between the 12th and 14th days on which estrogen hormone is at its highest level, were found to be 23 U/ml in healthy women and 40 U/ml in patients with tumors. These values are statistically significant, while CA 12-5 values determined in samples obtained on the 20th-25th days are within the normal range. Values of the CA 12-5 tumor marker during the estrogenic phase are important in the diagnosis, management and follow-up of cancer. Determination of estrogen hormone levels as an additional parameter may provide a significant correlation.

In the 1960's the work of Abelev, Gold and Freedman on tumor markers resulted in the clinical use of markers such as AFP, CEA, PAP. Ovarian specific antigen (CA 12-5), found as a result of investigations by Knapp and Bast, is considered as a specific antigen for non-mucinous epithelial cancers ([1]). It is a glycoprotein with a molecular weight of 500.000 daltons. Monoclonal globulin OC 125 was obtained by hybridization of murine splenic cells by epithelial ovarian cancer cells OVCA 433 celluler sequence ([2, 3]). This monoclonal globulin is used to determine CA 12-5 cancer antigen. These glycoproteins, resembling monoclonal antibodies, were first found in embryonic cells. They are not found in adult cells. But they are seen as a result of erroneous gene transcription coding proteins during malignant transformation of the adult cell. Studies by Buck *et al.*, in 1975 showed that glycoproteins contained in cells undergoing viral transformation include a greater amount of N-acetyl-neuramic acid (sialic acid) than that in control cells. The increase in the

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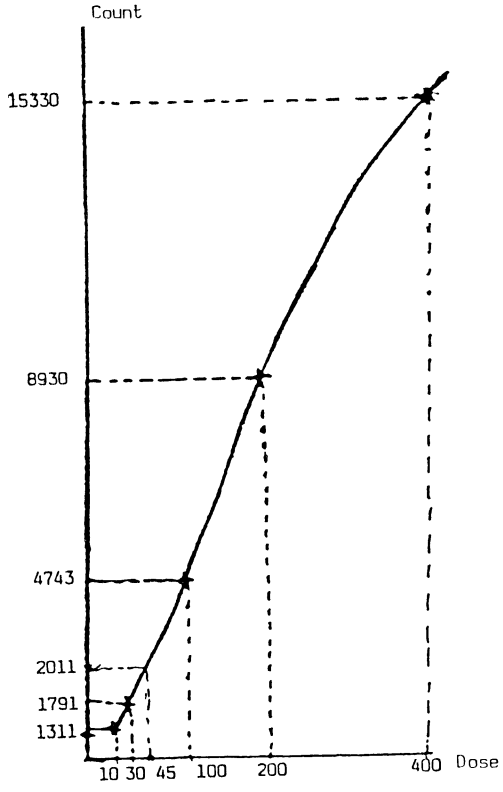

Fig. 1. – St. Curve of Count-Dose.

amount of sialic acid is proportional to tumor metastases ([4, 5, 6]).

CA 12-5 is a specific tumor marker in cases of ovarian tumors and the diagnosis of metastasis ([2, 7, 8, 9, 10, 11]). In addition, it is used in the follow-up response to chemotherapy in patients ([12]). This marker increases at definite rates in other malignancies, in benign diseases as well as in healthy individuals ([13, 14]). The amount of CA 12-5 tumor marker is directly proportional to the tumoral mass. But it is not related to tumor histology ([9, 15]). Its serum levels in healthy women are low, which supports the view that it is secreted by the female genital organs ([9]). The high CA 12-5 level in amniotic fluid specimens in the 3rd and 6th months of pregnancy suggests that it originated from stem cells ([16]). In contrast, values in the sera of pregnant women were found low ([17]).

Follow-up examination of CA 12-5 values gave favourable results in distinguishing endometrial cysts from benign non-endometrial cysts with laparoscopy and laparotomy; they have a diagnostic value ([18, 19]). In advanced breast cancer CA 12-5 values were found to be higher than CEA.

After removal of the endocrine system, low values were observed in these patients during regression. But in the case of metastases, values increased again ([11, 20]). The fact that CA 12-5 values as high as those in cases of ovarian tumors were found in the menstrual phase of healthy women ([21]) represents the basis of our study. Whether the amount of CA 12-5, which is one of various glycoproteins secreted by ovarian tumors, varies during each phase, playing an important part in the hormonal equilibrium of the organism both in healthy women and in tumor patients, was a subject for investigation. The present study was made in order to demonstrate that this marker was not only specific for ovarian tumors, but may also have a certain importance in other maligniancies, because CA 12-5 values were found to be correlated and significant in all phases, or in any phase.

MATERIAL AND METHOD

The sandwich model of the RIA method was used in order to determine CA 12-5 serum levels. A prospective study was made in the Insti-

Table 1. – *Data of Standard Surve.*

St.	Min.	Count	Dose
1	0.5	1311	10.0
2	0.5	1791	30.0
3	0.5	4743	100.0
4	0.5	8930	200.0
5	0.5	15330	400.0
I. Sample	0.5	2011	45.0

Table 2. – *Arithmetical Means of CA 12-5 values according to sample distribution.*

Samples		PHASES		
		Menstruation	Ovulation	Pre-Menstruation
Healthy Women	(30)	37.3±28 (41.8±37.1) [a]	21±17.6 (23.1±21.6) [a]	26.4±20.2 (28.3±22.3) [a]
Women with Tumor	(21)	46.9±37.6 (49±40) [b]	37.5±28 (39.8±31.7) [b]	30.4±16.3 (36.6±33.2) [b]
Breast Tumor	(13)	39.4±29.3 (42.6±33.9) [c]	32±26 (35.7±32.7) [c]	26.8±15.6 (36.8±40.4) [c]
Thyroid Tumor	(4)	25±19 (47.9±53.9) [d]	30.8±21.9 (33.2±23.5) [d]	33±20 (35.6±21.8) [d]

	AGE GROUPS								
	15-25	26-35	36-45	15-25	26-35	36-45	15-25	26-35	36-45
Healthy	40.4±34.5 (54±53.5) [a]	29±20.8	43.5±31	22.2±26.3 (25.6±30.6) [a]	20.1±15.4	24±18.5	23.2±23.8	23.1±20.8 (24.7±23.5) [a]	25.9±20.9
With Tumor	84.2±37.4	49.7±45.2 (54.7±50.2) [b]	33.4±22.2	60±29.3	35.4±30.2 (40.9±36.7)	32.6±25	43.9±11.3	33.7±12.0 (48.5±45.8)	23.8±18.3
Breast Tumor	—	41.5±30.9 (42±31.9) [c]	39.2±30.2	—	24.2±15.3 (34.3±36) [c]	30.4±18.2	—	28.4±7.4 (51.1±57) [c]	25.7±19.5
Thyroid Tumor	47	15.5±16.6 (56.9±73.2) [d]	22.2	52.8	33.6±16.8 (37.4±19.7) [d]	1.6	49.1	36.9±15.5 (42.5±14.4) [d]	1.6
Multiple Myeloma	—	—	36.9	—	—	81.8	—	—	25.8
Hodgkin	—	121.9	—	—	92.2	—	—	51.6	—
	—	83.6	—	—	34.8	—	—	30.9	—

[a] With the highest CA 12-5 value
[b] With the highest CA 12-5 value
[c] With the highest CA 12-5 value
[d] With the highest CA 12-5 value

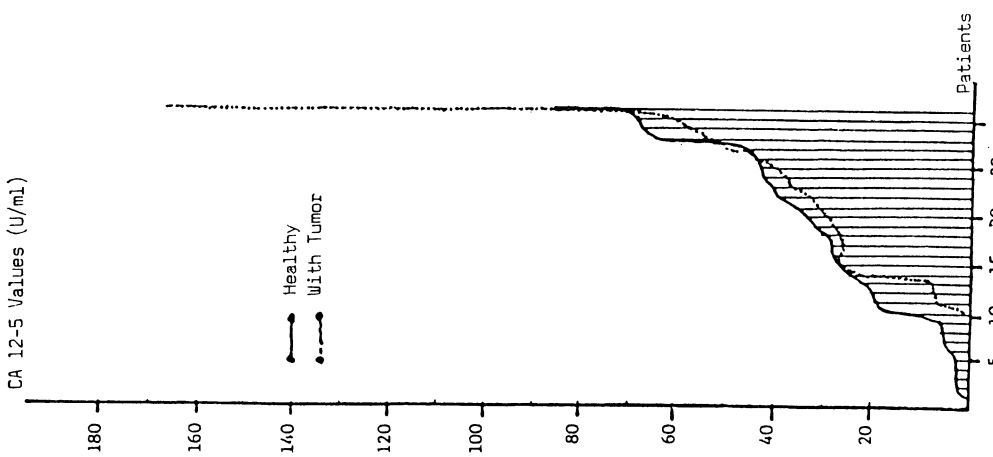

Fig. 4. – Distribution of CA 12-5 in premenstruation phase.

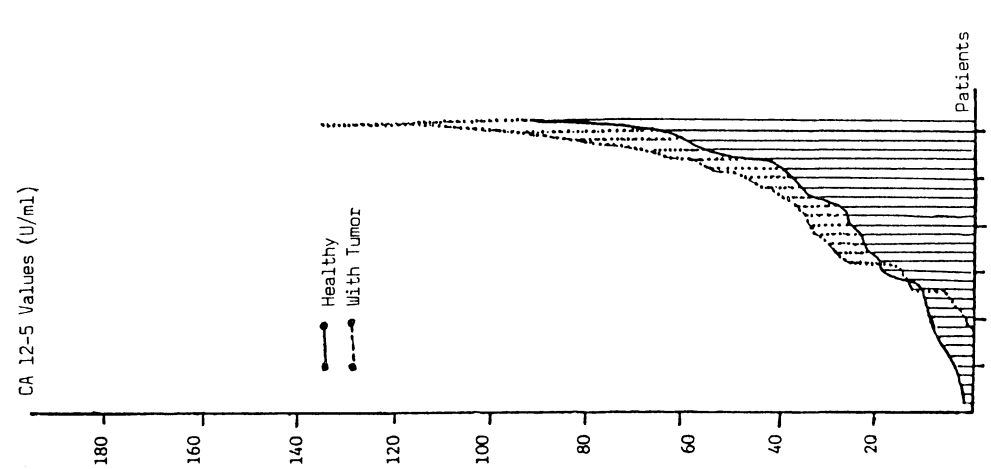

Fig. 3. – Distribution of CA 12-5 in ovulation phase.

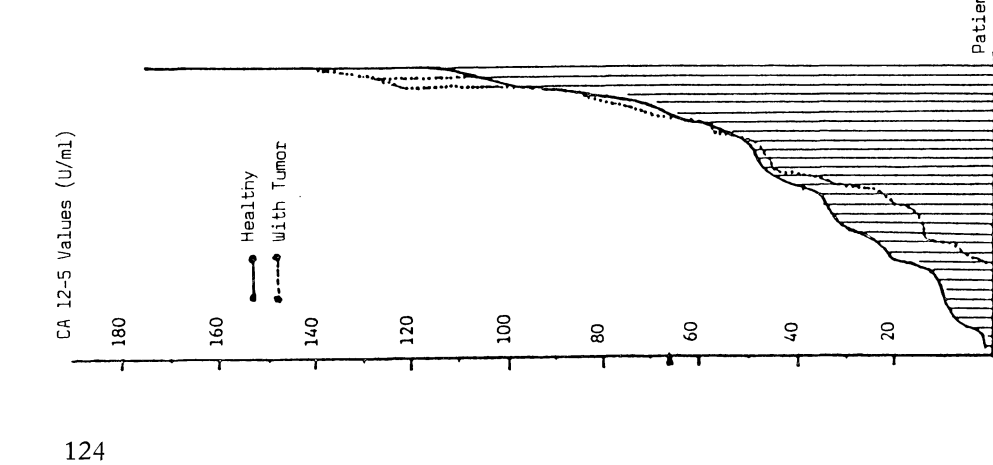

Fig. 2. – Distribution of CA 12-5 in menstruation phase.

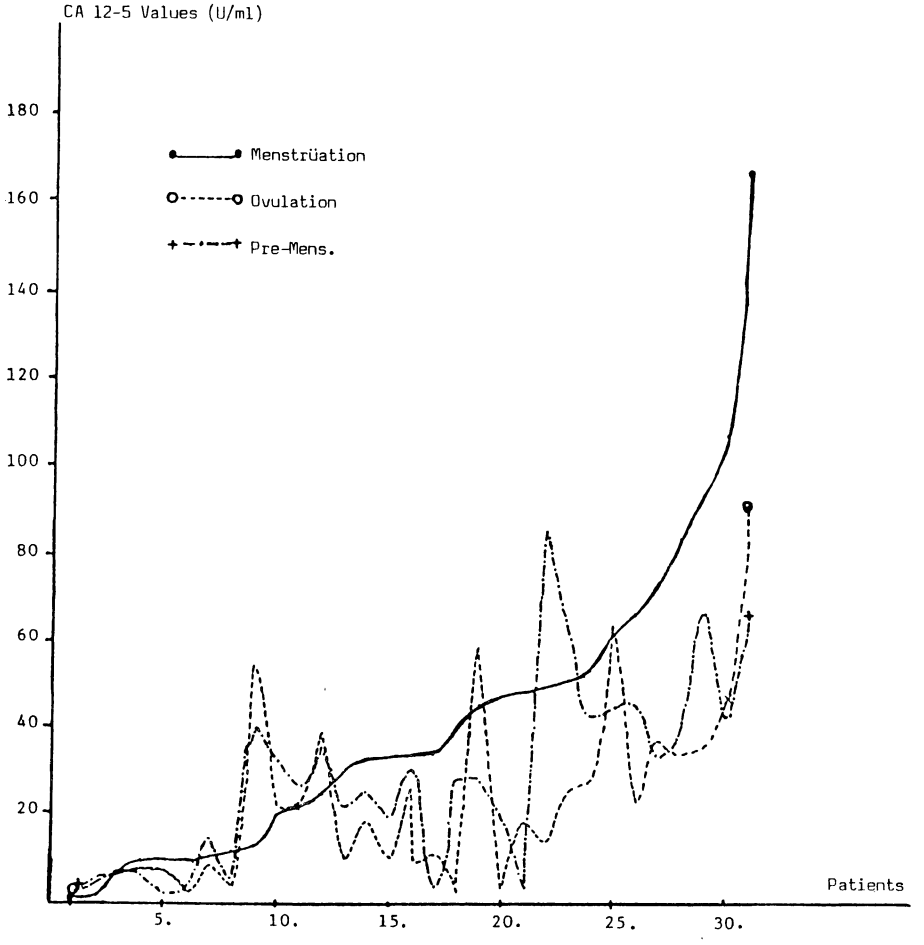

Fig. 5. – Distribution of CA 12-5 in three phases in the same healthy sample.

tute of Oncology of Istanbul University in 1988 in 31 apparently healthy women, aged from 15 to 25, 26 to 35, 36 to 45 and in 22 menstruating women patients belonging to the same age groups with non-gynecological tumors. Blood samples were obtained at random in a certain healthy population during menstruation (1st and 2nd days), ovulation (12th to 14th days) and pre-menstruation (20th to 25th days) phases. The sera were stored in −20 °C until a number of samples was reached. The same procedures were also performed for tumor patients.

Table 3. – *Results of Student t-test.*

Phases		t-value	P-value
Menstruat.	∞	1.08	0.3>p>0.2
Ovulation	∞	2.7	0.01>p>0.001 significant
Pre-Mens.	∞	0.34	0.9>p>0.5

RESULTS

The standard curve of CA 12-5 values of the samples and the data are shown in Table 1 and Figure 1.

The arithmetical mean values of CA 12-5 samples of 31 healthy and 22 men-

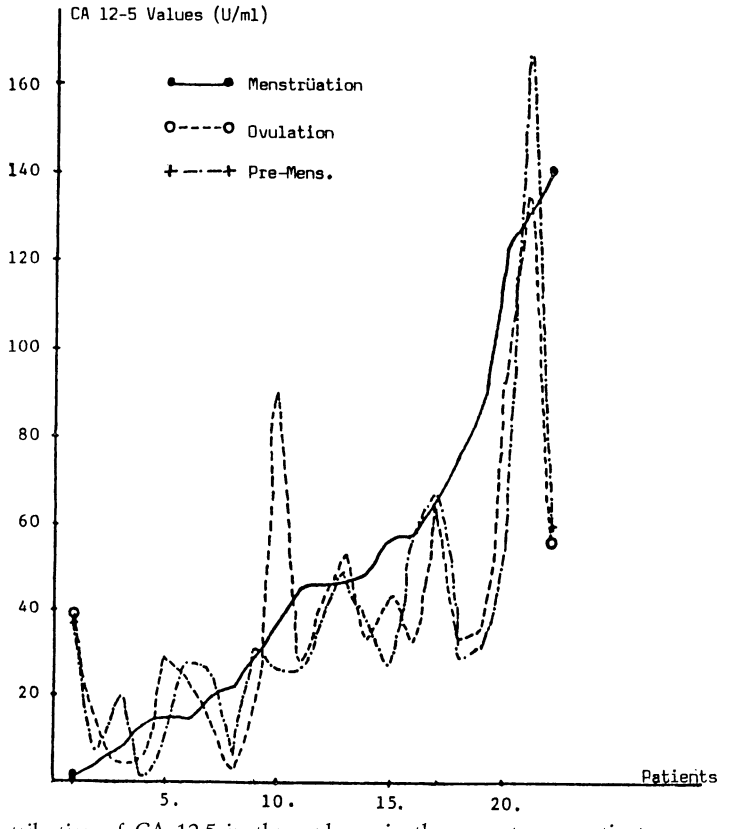

Fig. 6. – Distribution of CA 12-5 in three phases in the same tumor patient.

struating women with non-gynecologic tumors are shown in Table 2 according to sample distribution.

Statistical significance, estimated from values obtained in three phases of the menstrual cycle, is summarized in Table 3.

Table 4. – *Significance according to age and phases in patients with breast tumor.*

Age	Phase	t-value	P-value
	Menstruation ∞	0,75	0.3>p>0.5
26-35	Ovulation ∞	0.46	0.5>p>0.9
	Pre-Mens. ∞	0.73	0.3>p>0.5
	Menstruation ∞	0.31	0.5>p>0.9
36-45	Ovulation ∞	0.76	0.3>p>0.5
	Pre-Mens. ∞	0.1	0.5>p>0.9

It is noted in Figure 2 that there is no significant difference between the CA 12-5 values of blood specimens obtained on the 1st or 2nd day from both healthy women and tumor patients.

These values were in both cases superior to the upper limit. Figure 3 shows that estrogen hormone is at the highest level and that CA 12-5 values increase markedly in tumour patients compared with healthy women. The arithmetical mean values (Table 2) show a 75% increase regardless the standard deviation.

Figure 4 shows that there is not any significant difference between the CA 12-5 values of healthy women and those of tumor patients either in premenstrüal or menstrual phases (Tables 2, 3).

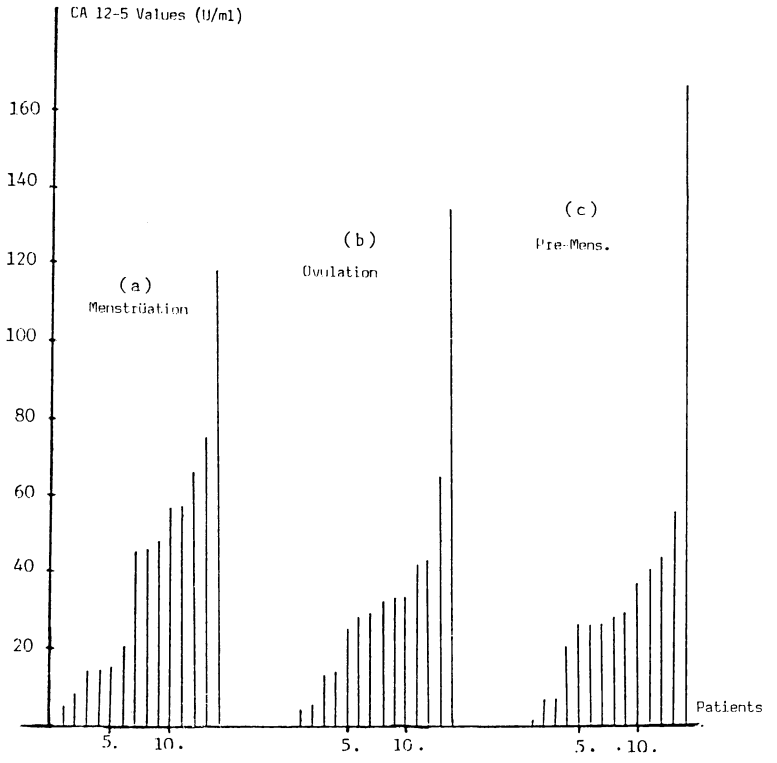

Fig. 7. – Distribution of CA 12-5 in three phases in women with breast tumor.

The distribution of CA 12-5 of the same sample in three phases is shown in Figure 5, and the distribution of CA 12-5 of the same tumoral sample is presented in Figure 4. In order to determine the significance of three-phase variations in these figures the menstruation, ovulation and premenstruation phases of the same sample are presented together. A correlated and significant variance is observed in three phases.

The CA 12-5 values of a group of patients with breast tumors are shown in Table 4 and on the basis of their arithmetic wean values it was concluded that they did not present any significance (Figure 7, table 2, 4).

CA 12-5 values of a group of patients with thyroid tumors and their significance are given in Figure 8 and Table 2.

No significant difference was found between the age groups of women with breast and thyroid tumors (Tables 2, 4, 5).

DISCUSSION

In the present study an attempt was made to determine whether CA 12-5 values in healthy women and patients with non-gynecological tumors during menstrual cycle phases were important in the diagnosis, management and follow-up of cancer. The results of this study support the hypothesis that mean CA 12-5 values in healthy women and in tumor patients are not dependent on age or sex.

In studies made up to the present time CA 12-5 values in the menstrual phase were found to be higher than 35 U/ml ([1]), which is considered the upper limit in cir-

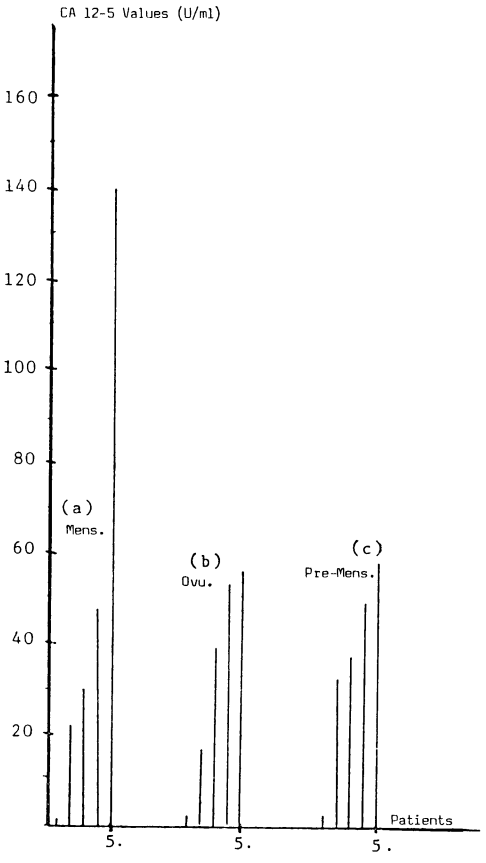

Fig. 8. – Distribution of CA 12-5 in three phases in women with thyroid tumor.

culation. In fact this value was given as 51 U/ml in literature ([17]). CA 12-5 values in infertile women were higher than 35 U/ml in the menstrual phase ([22]).

Consequently it was expected that CA 12-5 values obtained during the menstrual phase would be useful in the follow-up or diagnosis of cancer. Although values are not as high as 51 U/ml in the present study: they are 42 U/ml in healthy women and 49 U/ml in tumor patients.

CA 12-5 values have not so far been investigated during ovulation and the premenstrual phases which represent the important phases of the menstrual cycle. In our study also including these phases, the mean CA 12-5 values which are supposed to be at their highest levels between the 12th and 14th days are 23 U/ml in healthy women and 40 U/ml in tumor patients. This difference is statistically significant. CA 12-5 values in samples obtained during the premenstrual phase in which the progesterone hormone is at high level are within ithe normal range.

According to the results obtained from our study only the ovulation phase is significant among the phases of the menstrual cycle. During this phase CA 12-5 values are higher than the upper limit 35 U/ml, while in healthy women, they are at a very low level. On the basis of these findings it is thought that it is not necessary to determine CA 12-5 values during all the three phases of the menstrual cycle. Considering the treatments instituted in tumor patients it may be concluded that the serum levels of the CA 12-5 tumor marker only during the ovulation phase are more valuable in the diagnosis, management and follow-up of cancer, and that the recognition of estrogen hormone levels may be helpful as an additional parameter.

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