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Detection of Ovarian Cancer by Determination of Ca 125 in Different Patohistologycal Types of Tumor According to Age

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A B S T R A C T

During the eighteen-year period in »Sestre milosrdnice« University Hospital Center, Zagreb, 271 women with ovarian tumor was studied. 229 women with ovarian cancer and 42 with borderline tumor. The pathohistological types of tumors were different. The age of the patients ranged from 20–83 years. In all patients the value of biochemical marker CA125 was determined. The aim of this study was to determine the usefulness of CA125 measurement in different age groups and in different patohistologycal forms of tumor. CA125 has proven to be positive in 89.1% of women with ovarian cancer and in 62% with neoplasm of low malignant potential. The higher values of CA125 were detected in younger women with low malignant tumor potential. Serous and metastatic tumor types were also associated with higher values of CA125.

Key words: *ovarian tumor, pathohistological type, CA 125*

Introduction

Ovarian cancer has the leading mortality rate among gynecological tumors and it is a major challenge for gynecological oncology. The scant symptomatology is the reason of usually late diagnose and is the leading cause if death among gynecologycal cancers.

The risk for developing ovarian cancer during woman life is about 1.5%, and for dieing from it almost 1%[1]. It is the fifth cause of all cancer caused mortality in women[2]. Ovarian cancer requires extensive surgical treatment, intensive and often complex therapies. In the last decade, the incidence of ovarian cancer is growing[3]. Ovarian tumors are histogenetically, histologically and clinically very heterogeneous group. The origin of the most common types is the covering ovary epithelium (more than 90%), specialized reproductive cells and stroma. Epithelial ovarian tumors are the most common type of all ovarian tumors (65–75%) and of all malignant ovarian neoplasm (80–90%)[4] and are classified as benign, atypical proliferative (tumors of low malignant potential – LMP) and malignant tumors[5]. Histologycally, about 75–80% of all epithelial tumors are serous type. Less frequent types are mucinous and endometrioid tumor (10% each) and light cells cancer, Brenner tumor, and undifferentiated carcinoma (less than 1% each)[1]. The incidence of different ovary tumors and the best way for distinguishing benign from malignant changes considering anthropological parameters (height, weight, body mass index – BMI, parity, material status, education, age, menopausal status, rural *versus* urban resistance, qualitative dermatoglyphic traits) have been studied [6,7]. For the detection of ovarian cancer were also examined various diagnostic methods (X-ray, CT, MR), but the most widely used are: ultrasound, color doppler and biochemical markers, most of which CA 125. Also, to effectively discern what kind of the tumor is present, the different combinations of these parameters were investigated. The most famous circulating antigen found in women with ovarian cancer is CA 125, with sensitivity 85–96%[8,9]. Serum level of this marker is determined using monoclonal antibodies. About 83% of patients with epithelial ovarian cancer have ele-

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vated level of CA125: 50% in stage I, 60% in stage II, and over 90% in advanced stages[10]. CA 125 is used for assessment of the effectiveness of surgical and chemotherapy treatment[11]. For some types of the tumor (borderline and malignant mucinous tumors, serous borderline) sensitivity of CA 125 is significantly comparing to the invasive serous cancer. The aim of our study was to determine the usefulness of marker CA 125 in detecting ovarian cancer in patohistologycally different tumor types.

Materials and Methods

The survey was conducted in »Sestre milosrdnice« University Hospital Center, Zagreb, during 18-year period. 271 women with ovarian tumor were included (229 with malignant and 42 with LMP). All patients were surgically treated.

The preoperative treatment included determination of serum marker CA 125 using a monoclonal antibody (Vitros Immunodiagnostic Products CA 125 II Reagent Pack, Ortho Clinical Diagnostics). Limit value for CA125 in the laboratory of our Clinic is 35.0U/ml, mean values <35 U/ml are considered physiological, while those above that value are considered pathological. After pathophsyological verification of tumor, patients with malignant tumors and low malignant potential (LMP) were determined.

Patients were divided regarding age and histopathologic type of the tumor.

In these groups we questioned the marker CA 125 level according to hystological type. In particular, we examined the incidence of certain types of malignant tumors considering the age and value of CA125. The number of true positive and false negative Ca 125 results in specific histopathological types of tumors was calculated. Interestingly, changed incidence of certain types of tumor over a period of 18 years is found.

TABLE 1
PATHOHISTOLOGIC TYPES OF TUMORS

1. Endometrioid
2. Granulosacellular
3. Serous
4. Mucinous
5. Serous (LMP)
6. Metastatic
7. Clarocellular
8. Anaplastic
9. Mucinozni (LMP)
10. Teratoma
11. Mixed mezodermal
12. Granulosa cellular (LMP)
13. Tubar
14. Endometrioid (LMP)
15. Mixed epithelial

Descriptive statistics and frequency distributions were performed. In order to analyse differences in age or differences in CA 125 values for different tumor type series of one-way ANOVA were performed. The p-value was set at 0.05.

Results

During 18 years period in the »Sestre milosrdnice« University Hospital Center the research involved 271 women, 229 with ovarian cancer and 42 with atypical epithelial proliferative tumor (LMP). Patients aged between 20 and 83 years, had 15 different tumor types patohistologycally verified, (Table 1) and different incidence of certain types during that period (Table 2).

During 1993 the highest incidence had serous carcinoma (44.5%). During the next 10 years period (1994–2004) the highest incidence had endometrioid tumor type. After 2004 the occurence of serous carcinoma grew again and in the past year (2010). Malignant endometriodes tumor type predominates.

The frequency of the three most common histological types of ovarian cancer in our sample is shown in Figure 1.

The average age of all examined patients was 57.9 years. Due to the patohistologycal result the incidence of malignant and low malignant potential tumor was different according to the age. Patients with malignant disease were somewhat older (mean 59.3 years, 30–83 years, sd 11.7) (Figure 2).

Patients with LMP were younger (mean 50 years, sd 16.45) (Figure 2).

The age difference is statistically signifficant. ($F(14.256) = 2.49$, $p<0.01$).

CA 125 level did not show statistically significant difference with respect to pathohistological type of tumor ($F(10.218) = 0.83$, $p>0.05$). The number and percentage of true positive and false negative results of marker CA

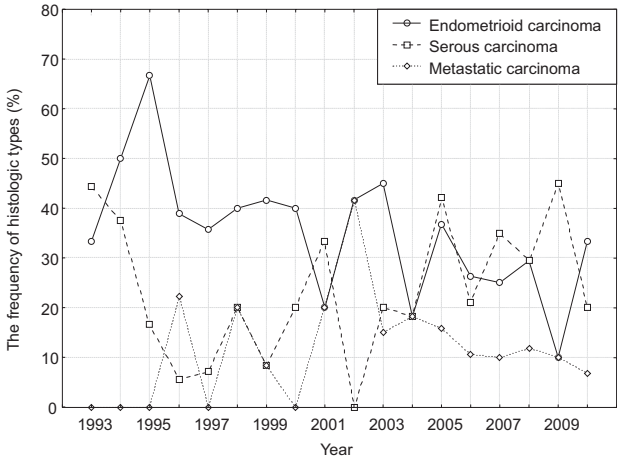

Fig. 1. The frequency of the three most common histological types from 1993–2010.

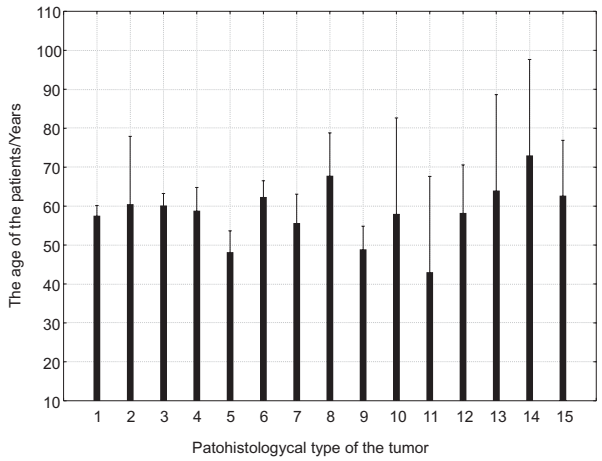

Fig. 2. The age of the patients regarding to the patohistologycal type.

125 with respect to the types of malignant tumors is shown in Table 3. In group with malignant tumor we can not abstract the age group in which the percentage of true positive was significantly higher (Table 4).

The highest percentage of true positive results (over 90%) in patients with serous and metastatic cancers was observed (with the exception of few histopathological types insufficient for statistical analysis).

As for LMP tumors, the percentage of true positive results is far less, only 62% according to our results (Table 5).

Discussion

Ovarian cancer is common disease with high mortality. Symptoms of the disease occur late, when the disease is already extended, the treatment options modest and the results are often poor. For all these reasons there is a need to optimize early detection techniques, and to examine the value of existing methods for detecting ovarian cancer.

Tumor markers are molecules occur in blood, urine or tissue of patients with certain types of cancer in higher concentrations than normally.

The ideal tumor marker would be: the one that can be detected in blood, urine or tissue; which is positive only in patients with malignant disease; whose concentration coincides with the stage of the disease and response to treatment; which is secreted in only one tissue and is easily measured. Unfortunately, no tumor marker has yet met this ideal. Literature suggests CA 125 level to be most reliable for distinguishing benign from malignant ovary[12] and borderline tumors. The higher values are registered in patients with advanced stages of the disease[10,13].

Mean values of CA125 were significantly higher in patients with malignant compared to benign ovary changes. The cut-off value 35 U / ml is sufficient for diagnose about 80% of ovarian cancer. CA 125 has proved to be more reliable variable for identifying malignant tumor in relation to colored doppler tehnicque in women over 35 years of age.

TABLE 2
THE FREQUENCY OF HISTOLOGIC TYPE FROM 1993–2010

year	PHD															
	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.	sum
1993.	3	1	4	1	0	0	0	0	0	0	0	0	0	0	0	9
1994.	4	0	3	0	1	0	0	0	0	0	0	0	0	0	0	8
1995.	4	0	1	0	1	0	0	0	0	0	0	0	0	0	0	6
1996.	7	0	1	4	1	4	1	0	0	0	0	0	0	0	0	18
1997.	5	1	1	1	0	0	1	3	1	1	0	0	0	0	0	14
1998.	6	0	3	2	1	3	0	0	0	0	0	0	0	0	0	15
1999.	5	0	1	4	0	1	0	0	0	0	1	0	0	0	0	12
2000.	4	0	2	0	2	0	1	0	1	0	0	0	0	0	0	10
2001.	3	0	5	1	1	3	1	0	1	0	0	0	0	0	0	15
2002.	5	0	0	0	0	5	1	0	1	0	0	0	0	0	0	12
2003.	9	0	4	0	2	3	0	0	1	0	0	1	0	0	0	20
2004.	4	0	4	0	1	4	1	0	4	0	0	3	1	0	0	22
2005.	7	0	8	0	1	3	0	0	0	0	0	0	0	0	0	19
2006.	5	0	4	1	2	2	0	0	3	0	0	0	0	1	1	19
2007.	5	0	7	0	0	2	3	1	2	0	0	0	0	0	0	20
2008.	5	0	5	1	1	2	1	0	1	0	0	0	0	0	1	17
2009.	2	0	9	1	4	2	0	1	1	0	0	0	0	0	0	20
2010.	5	0	3	1	2	1	1	0	1	0	0	0	0	0	1	15
SUM	88	2	65	17	20	35	11	5	17	1	1	4	1	1	3	271

TABLE 3
THE NUMBER OF TRUE POSITIVE AND FALSE NEGATIVE RESULTS DUE TO THE TYPE OF MALIGNANT TUMOR

PHD	total	false negative N (%)	true positive N (%)
1. Endometrioid carcinoma	88	13 (14.8)	75 (85.2)
2. Ganulosacellular carcinoma	2	1 (50)	1 (50)
3. Serous carcinoma	65	4 (6.2)	61 (93.8)
4. Mucinous carcinoma	17	4 (23.5)	13 (76.5)
6. Metastatic carcinoma	35	1 (2.9)	34 (97.1)
7. Clarocellular carcinoma	11	2 (18.2)	9 (81.8)
8. Anaplastic carcinoma	5	0 (0)	5 (100)
10. Solid carcinoma	1	0 (0)	1 (100)
11. Mixed mesodermal magninant tumor	1	0 (0)	1 (100)
13. Tubar carcinoma	1	0 (0)	1 (100)
15. Adenocarcinoma mixtum	3	0 (0)	3 (100)
total	229		

TABLE 4
THE NUMBER OF TRUE POSITIVE AND FALSE NEGATIVE IN MALIGNANT TUMORS WITH RESPECT TO THE AGE

age groups	total	false negative N (%)	true positive N (%)
<30	1	0	1 (100)
31–40	12	2 (16.7)	10 (83.3)
41–50	45	4 (8.9)	41 (91.1)
51–60	65	8 (12.3)	57 (87.7)
61–70	62	5 (8.1)	57 (91.9)
>70	44	6 (13.6)	38 (86.4)
total	229		

TABLE 5
THE NUMBER OF TRUE POSITIVE AND FALSE NEGATIVE IN LMP TUMORS WITH RESPECT TO THE AGE

age groups	total	false negative N (%)	true positive N (%)
<30	7	1 (14.3)	6 (85.7)
31–40	5	1 (20)	4 (80)
41–50	10	5 (50)	5 (50)
51–60	9	3 (33.3)	6 (66.7)
61–70	5	3 (60)	2 (40)
>70	6	3 (50)	3 (50)
total	42		

For monitoring the course of illness CA 125 proved to be a very good marker. Alvarez and colleagues[14] state the literature data about CA 125: good correlation with the disease with increasing value while progression and lowering value while regression of the disease. Other authors[15] agree that boosting levels of CA 125 are in very good correlation with the disease progression.

The most common type is the group of epithelial ovarian cancer (90%). The literature data suggest that 75–85% of epithelial cancer group are serous type, and rarely mucinous and endometrioid type (10%)[1]. Contrary to these data our eighteen years survey found endometrioid carcinoma to be the most common histological type (1994.–2004.). Serous type dominates at the beginning of the research (1993) and after 2004. during next six years, after which endometrioid type is the leading type again. Some authors in their research have also noted that the incidence of certain histological types of tumor is variabile[16]. In our study the average age for occurrence of LMP and malignant types of tumor was 57.9 years, slightly higher in patients with malignant form (59.3 years), and slightly lower in patients with borderline tumors (50g). Such observations have already been reported in the literature[1]. Accordingly, our patients with serous and mucinous borderline tumors were statistically significantly younger than the other investigated groups. Since we noted only one woman with endometrioid LMP tumor, conclusion regarding occurence age is not possible.

For us the most important is an answer to the question of how much we can actually rely on the biochemical marker CA125.

We confirmed the literature results about high reliability of CA 125 marker showing high percentage of true positive (89.1%) and false negative result (10.9%) in patients with malignant ovary tumors (cut off value 35 U/ml)[17]. The highest percentage of true positive results was found in patients with serous and metastatic malignant tumor types (apart from the group with insufficient number of patients). Other authors had similar observations in their research[18].

Although we expected stronger response and therefore maybe higher values of CA125 in younger women we did not get such results. On the contrary, some authors have

noted a higher specificity, sensitivity and the percentage of true positive results in older, postmenopausal women[17].

In our patients with malignant tumors, we can not single out any particular age group with significantly higher percentage of true positive results. (Of course, the group of patients younger than 30 years was excluded since there was only one patient in that group).

As for tumors of low malignant potential, the authors agree that the percentage of true positive CA 125 value is far less reliable in relation to malignant tumors[19] and its value depends on the stage of the disease. Our results on 42 patients with borderline tumors show only 62% true positive values (Table 5).

It should be noted that two groups with youngest patients have a higher percentage of true positive results but since we have small number of such patients the difference regarding age can not be statistically confirmed. We believe that our observation will be statistically confirmed in further research.

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PREPOZNAVANJE RAKA JAJNIKA ODREĐIVANJEM CA 125 KOD RAZLIČITIH PATOHISTOLOŠKIH TIPOVA TUMORA S OBZIROM NA DOB

SAŽETAK

Tijekom 18-godišnjeg perioda u Kliničkom bolničkom centru »Sestre milosrdnice« u Zagrebu ispitana je 271 žena sa tumorom jajnika od čega ih je kod 229 dijagnosticiran karcinom jajnika,a kod 42 tumor niskog zloćudnog potencijala (»borderline« tumor). Patohistološki tipovi tumora su različiti. Uključene su ispitanice od 20–83 godina starosti. Kod svih pacjentica određen je tumorski marker CA 125. Cilj istraživanja bio je odrediti korisnost mjerenja markera CA 125 u različitim dobnim skupinama i različitim patohistološkim tipovima tumora. U zaključku: CA125 je pozitivan u 89,1% žena sa karcinomom jajnika i u 62% žena sa neoplazmom nisklog malignog potencijala. Više vrijednosti CA125 nađene su kod mlađih žena sa neoplazmom niskog malignog potencijala. Serozni i metastatski tumori su povezani sa višim vrijednostima CA125.