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# LEVELS OF CA125 MARKER IN PATIENTS WITH DIFFERENT HISTOLOGIC TYPES OF OVARIAN CANCER

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**Abstract:** Ovarian cancer is one of the most lethal cancers among women worldwide. The most used tumor marker in ovarian cancer is CA 125, elevated levels of CA 125 having been recorded in 80% of patients with advanced stages of the disease. The objective of the present study was to evaluate and compare CA 125 levels in relation with different histologic types of ovarian cancer. We analyzed 124 women diagnosed with ovarian cancer between 2010 and 2016. Four parameters were investigated: age at diagnosis, level of CA 125 at diagnosis, histologic type and location of the tumor. The results show a mean age at diagnosis of 50.29 ± 9.83 years. The serous ovarian cancer was the most frequent histologic type (45.97%). Highest mean levels of CA 125 were recorded in endometrioid (335 U/ml) and serous (792,48 U/ml) tumors. Lower levels were registered in clear cell (139,9 U/ml) and mucinous (169,49 U/ml) tumors.

## INTRODUCTION

In developed countries, ovarian cancer is the 5th most common cancer among women and the 7th worldwide (Torre et al., 2015 ; Bray et al., 2015). Around the world almost 239.000 new cases of ovarian cancer are diagnosed each year. With over 151.000 deaths per year worldwide, ovarian cancer is the 8th most fatal female cancer in the world (Torre et al., 2015). In the United States, ovarian cancer is the one of the most lethal malignancy, with over 14.000 deaths in 2015 (Siegel et al., 2015). The new ovarian cancer estimated cases for 2016 in the United States are over 22.000 (Siegel et al., 2016). According to Canadian Cancer Society, in 2015 nearly 2.800 women were diagnosed with ovarian cancer and the number of deaths due to this disease were 1.750 (http://www.cancer.ca/en/cancer-information/cancer-type/ovarian/statistics/?Region=on). In Europe, ovarian cancer is the 14th most common malignancy with 65.500 new cases diagnosed in 2012, the highest incidence being in Central and Eastern Europe, with over 28.000 cases (Ferlay et al., 2013). All this data show that, despite the advanced chemotherapy and new surgical procedures, the numbers are still high as well for incidence as for mortality.

The 5-year survival in patients with ovarian cancer is still below 45% (Urban et al., 2016). The majority of ovarian cancers remain clinically silent and almost 75% of patients are diagnosed in advanced stages (Zhu Lan et al., 2016). The cure rate for patients diagnosed in first stage of malignancy is almost 90% (Digant Gupta and Christopher Lis, 2009). Hence, the detection of the disease in the first stage has a decisive impact on survival rate (Negură L. and Negură A., 2016). A variety of biomarkers have been developed for an early detection of the ovarian cancer: CA 19-9, CA 15-3, CA 549, CA 125. From all of these biomarkers, CA 125 is the most utilized and it is regarded as gold standard tumor marker in ovarian cancer (Digant Gupta and Christopher Lis, 2009; Anastasi et al., 2013). CA 125 is a high molecular weight glycoprotein and it is expressed by fetal amniotic and coelomic epithelium (Negură A., 2008). In adult tissues, it is originate from the coelomic and Mullerian epithelia (Digant Gupta and Christopher Lis, 2009). His structure possess 2 major antigenic domains, A and B, which bind monoclonal antibodies OC125 and respectively M11 (Digant Gupta and Christopher Lis, 2009).

Before 2008, the only Food and Drug Administration (FDA) – approved ovarian cancer biomarker was CA 125 (Li et al., 2012). Elevated levels of CA 125 were recorded in 80% of patients with advanced ovarian cancer stages (Li et al., 2012). Also, high levels of cancer antigen 125 were found in benign gynecological diseases and non-gynecological cancers (Zhu Lan et al., 2016). Today, a value of CA 125 below 35 U/mL is considered normal (Digant Gupta and Christopher Lis, 2009). The important role of cancer antigen 125 in early exposure of ovarian cancer it is summarized in reports indicating that elevated levels of CA 125 are registered with 3 months before clinical detection (Digant Gupta and Christopher Lis, 2009 ; Zhang et al., 2015). Several studies indicates the usefulness of this biomarker in monitoring the treatment, disease progression and patient prognosis (Woo Dae Kang et al., 2010).

The NICE guidance indicate that serum CA 125 should be the first test performed on women with suggestive symptoms of ovarian cancer ( Moss et al., 2013).

The objective of this study is to evaluate and compare CA 125 levels in relation with different histologic types of ovarian cancer.

## MATERIALS AND METHODS

This is a retrospective study of 126 women diagnosed with ovarian cancer between 2010 and 2016. All data were collected from database of the Oncogenetics Departament, University of Medicine and Pharmacy Gr.T.Popa Iași, and from medical records of the Oncology Clinic, Regional Institute of Oncology, Iași. The study had the approval of the Ethical Committee of the University of Medicine and Pharmacy Gr.T.Popa Iași. We analyzed four parameters: age at diagnosis, level of CA 125 at diagnosis, histologic type and location of the tumor. All the patients with Krukenberg tumors, benign tumors or metastasis to the ovaries were excluded from the study. The value of CA 125 accepted as normal in this study was 0-35 U/ml. The statistical data are expressed as mean ± standard deviation.

## RESULTS AND DISCUSSION

Of the initial 126 patients, only 124 fulfilled the requirements and were included in the study. The mean and the median age at diagnosis are shown in Table 1.

Table 1. Age at diagnosis for ovarian cancer cases (N=124).

| | |
|---|---|
| Mean age of diagnosis | 50,2984 |
| Median age of diagnosis | 51,0000 |
| Std. Deviation | 9,83686 |
| Minimum | 17,00 |
| Maximum | 76,00 |

According to American Society of Clinical Oncology (ASCO), 68% of women with ovarian cancer are older than 55 and 32% are younger than 55 (http://www.cancer.net/cancer-types/ovarian-cancer/risk-factors-and-prevention). In the United States, the median age at diagnosis is 63 (http://seer.cancer.gov/statfacts/html/ovary.html). Chan et al., published in 2006, a study on 28.165 American women diagnosed with primary epithelial ovarian cancer. The median age in his report was 64 years ( Chan et al., 2006). Recent data published by Praestegaard et al. on 10.601 women from different world regions (Australia, Europe and United States),diagnosed with epithelial ovarian cancer, showed a median age at diagnosis of 57 years (Praestegaard et al., 2016). A case-control research of ovarian cancer in African American women conducted by Schildkraut et al. showed a mean age at diagnosis of 57,4 ± 11,2 years (Schildkraut et al., 2014).In Sweden the mean age at diagnosis is 62,4 ± 7,4 years (Riman et al., 2004).

In Romania, there are very few available ovarian cancer data. Similar to the present study, a mean age of 51,46 ± 14,28 years was found on 82 Romanian women diagnosed with ovarian cancer by Furau et al. (Furau et al., 2011). Another study, published in 2012 by Voicu et al. on 50 Romanian women diagnosed with ovarian cancer, shows a mean age of 54,44 ± 13,84 years (Voicu et al., 2012). All these results indicate that we obtained a lower mean age at diagnosis for ovarian cancer than other reports from countries like USA, Australia or Western Europe. On the contrary,

the similarity between our data and those presented in other Romanian studies, may indicate that Romania has a lower mean age at diagnosis for ovarian cancer than Western countries.

From Fig. 1, we can notice that in our study the highest ovarian cancer rate (42,74%) was in women aged 51-60 years. Same results have been obtained by Furau et al. In their study, the highest incidence of ovarian cancer was in 51-60 years group (Furau et al., 2011). According to International Agency for Research on Cancer (IARC), in Romania the peak rate of the ovarian cancer is in 60-69 years group (http://eco.iarc.fr/eureg/). In the United Kingdom, 53% of cases diagnosed with ovarian cancer are women aged 65 or more. The highest number of cases (965 cases) are in 65-69 years group (http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancertype/ovarian-cancer/incidence#heading-One; Jacobs et al., 2016). The highest percent (23,8%) of new ovarian cancer cases, in the United States, is in 55-64 age group (http://www.ovariancancer.org/about/statistics/). In Canada, in 2010, the highest incidence of ovarian cancer, was in women aged 85 and older, with a rate of 46,1 new cases per 100.000 women (Tanya Navaneelan, 2015). Fox et al., developed a study on 112 Canadian women with known diagnosis of high grade serous ovarian cancer. The mean age at diagnosis was 58,04 ± 10,54 years and the highest numbers of cases (37,5%) were in 50-59 years group (Fox et al., 2015). Data published in 2010 by Park et al. shows that in 2007 the highest ovarian cancer rate, was in Korean women aged 65-79 years (Park et al., 2010). In Australia, in 2016 it is expected the incidence of ovarian cancer will increase with age, until age group 65-69 (https://ovarian-cancer.canceraustralia.gov.Au/statistics). Our results in mean and group age show a lower age at diagnosis than other Western countries, but very similar with studies developed in Romania. At the same time, our records are inconsistent with data published by IARC. Further studies are needed to confirm this facts.

Table 2. Location of the tumor for ovarian cancer cases (N=124).

| Location of the tumor | | | | | |
|---|---|---|---|---|---|
| | | Frequency | Percent | Valid Percent | Cumulative Percent |
| Valid | Unspecified | 36 | 29,0 | 29,0 | 29,0 |
| | Left | 22 | 17,7 | 17,7 | 46,8 |
| | Right | 29 | 23,4 | 23,4 | 70,2 |
| | Bilateral | 37 | 29,8 | 29,8 | 100,0 |
| | Total | 124 | 100,0 | 100,0 | |

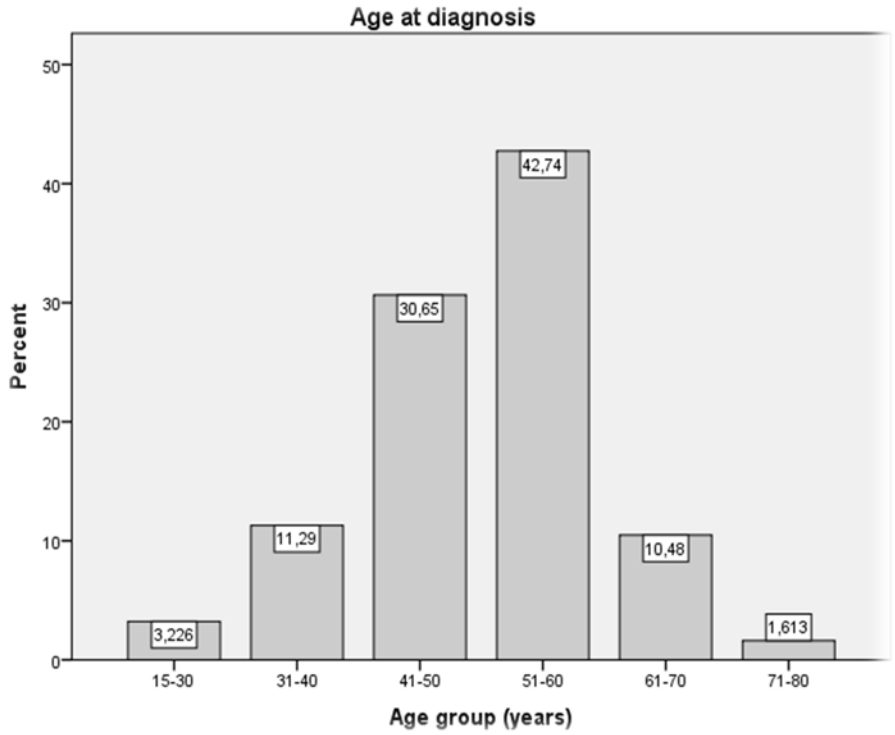


Figure 1. Structure of our patients lot by groups of age.

From table 2 we can observe that, the right ovary has developed cancer in 29 cases (23,4%). In 36 cases (29%), we were unable to establish the correct location of the tumor. Bilateral location reached the maximal frequency (29,8%). The lowest occurence was in unilateral left ovarian cancer (17,7%).

Fig. 2 indicates the main histologic types found in our study. The serous ovarian cancer was the most frequent histologic type (45,97%). Unfortunately, more than 18% of all cases had an unspecified histologic type.

Data published by Oberaigner et al., from 69 European cancer registries, reveal that overall proportions of the serous, mucinous, germ cell, other tumors and not otherwise specified, were 45,8%, 10,1%, 1,5%, 35,9% and 6,8% respectively. The highest rate of serous ovarian cancer were in Iceland (60.4%). The largest number of mucinous ovarian cancers were in Italy with 17,9% (Oberaigner et al., 2012). Similar data were obtained in Sweden by Riman et al., on 655 cases of epithelial ovarian cancer. They have identified 337 cases of serous ovarian cancer (51%), 60 cases of mucinous tumors (9%), 180 cases of endometrioid tumors (27%), 43 cases of clear-cell tumors (7%) and 35 cases of undifferentiated or others tumors (5%). The mean age at diagnosis for every histologic type was: 62,6 ± 7,3 years for serous tumors, 62,5 ± 7,8 years for mucinous tumors, 61,6 ± 7.6 years for endometrioid tumors and 61,2 ± 7,2 years for clear-cell tumors (Riman et al., 2004).

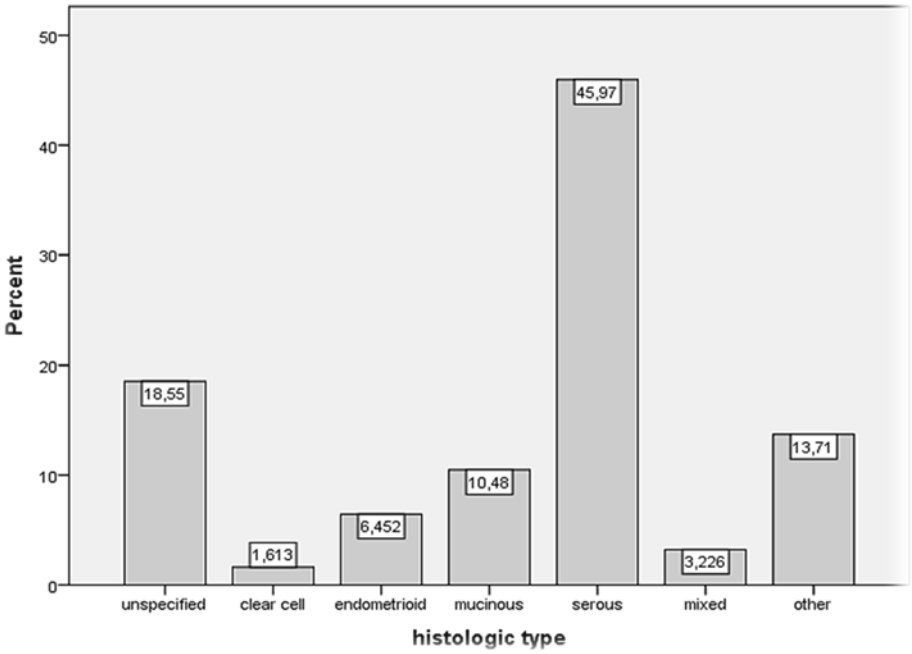


Figure 2. Structure of our patients lot by histologic subtypes of ovarian cancer.

In our study, the mean age for serous tumors was 48,91 ± 8,51 years. It is clear that our data indicate a similar proportion of histologic subtypes of ovarian cancer with other studies, but the mean age of serous tumors, in our study, is lower.

Fig. 3 shows the mean levels of CA 125 in different histologic types of ovarian cancer. Much higher values were obtained by Thakur et al., in a study on 40 patients with epithelial ovarian cancer. They presented high mean levels of CA 125 in serous adenocarcinoma (1571 ± 121,5 U/ml) and endometrioid carcinoma (2853 ± 136 U/ml). Mucinous adenocarcinoma and clear cell carcinoma had lower mean levels of CA 125: 775 ± 78 U/ml and 60 U/ml (Thakur et al., 2003). Our levels of CA 125 are much lower than those presented by Thakur et al. and the proportion is similar, except for endometrioid carcinoma. They presented very high mean levels of CA 125 in endometrioid carcinoma, but, in our study the highest mean level of CA 125 was in serous adenocarcinomas. Lower levels of CA 125 were recorded in mucinous and clear cell carcinoma, but all these levels were much higher than 35 U/ml.Similar results to ours, were obtained by Będkowska et al. in a reasearch on 110 epithelial ovarian cancer patients. In their case, the highest levels of CA 125 were in serous epithelial group (the median of CA 125 levels was 171,24 U/ml). The median of CA 125 levels in endometrioid epithelial group, was 114,24 U/ml (Będkowska et al., 2015).

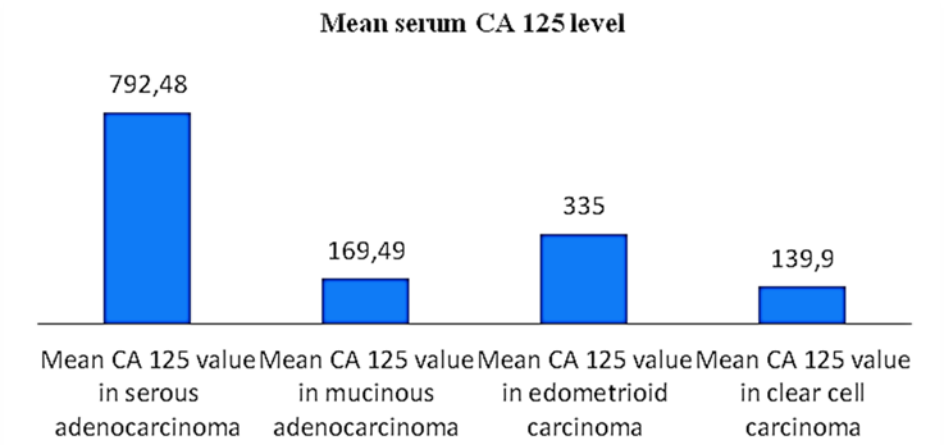


Figure 3. Mean levels of CA 125, by histological types of ovarian carcinoma.

This evidence confirm the utility of CA 125 in early diagnosis of ovarian cancer. Detection of high levels of CA 125 in women with no clinical signs, should be followed by other investigation, in order to exclude an ovarian malignancy. Also, our study suggests that CA 125 may have a role in early prediction of histological sub-types of ovarian cancer but additional studies should be performed to evaluate this possibility.

## CONCLUSIONS

Ovarian cancer remains a challenge for the medical world. Our data have a proportional similarity with other studies, except for the age at diagnosis. In our study, the mean and median age at diagnosis (50,29/51 ± 9,83 years) seems to be lower than other reports. Countries like USA, Canada or Western Europe have a mean age at diagnosis over 60 years. Same differences are in age groups: our data indicates the highest ovarian cancer incidence in 51-60 years group.

The mean serum CA 125 levels are very high, especially in ovarian serous adenocarcinoma. The mucinous and clear cell tumors have a lower level of serum CA 125 than serous or endometrioid adenocarcinoma, which is consistent with literature data. Although numerous new biomarkers have been identified, CA 125 reamains the gold standard biomarker in early detection of ovarian cancer.

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