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Prognostic impact of serum markers and BRCA mutation on histological types of ovarian cancer

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Abstract

Morbidity of ovarian cancer has been increasing for years. The lack of specific and sensitive methods of diagnosis causes delays in diagnosis. The most frequently used markers in the diagnostic process are CA125, HE4 and the Risk of Ovarian Malignancy Algorithm (ROMA). The aim of the study was to evaluate the correlation between the value of markers used in primary diagnosis of ovarian cancer and histological type of cancer and genetic status of patients with ovarian cancer.

Materials and Methods: The analysis was based on 55 patients from the clinic with a diagnosis of ovarian cancer with mean age 60.78±12.99 (median: 63.25 years). Each patient underwent surgical treatment. In every case tissue of ovarian tumor was investigated for BRCA mutation using NGS (next generation sequencing) methods.

Results: Level of CA125 at the time of diagnosis was statistically significant for serous (p=0.006) and endometrioid (p=0.01) ovarian cancer. A significant level of HE4 was observed in serous ovarian cancer (p = 0.021). There was a significant correlation between the calculated value of the ROMA algorithm and serous type of ovarian cancer (p=0.02).

Conclusion: CA125, which is correlated with histological type of tumor, has a significant role in monitoring the effectiveness of chemotherapy. Presence of BRCA mutation is a risk factor of morbidity of ovarian cancer and is not restricted to only one histological type. This is a preliminary report, which will be continued.

Keywords: Ovarian cancer; BRCA mutation; CA125 in ovarian cancer; HE4 in ovarian cancer

Introduction

Ovarian cancer is the fourth most common neoplastic disease in women. Morbidity has been increasing for years. In Poland over 3500 new diagnoses are made every year. In most cases ovarian cancer is diagnosed in an advanced stage due to lack of symptoms in the early stage of disease. The lack of specific and sensitive diagnostic methods causes delays in diagnosis. The most frequently used laboratory test is cancer antigen 125 (CA125), which is a protein used to assess the risk of ovarian cancer diagnosis and follow up the treatment [1]. CA125 was first described in the 1980s as carbohydrate antigen 125. The upper limit of CA125 in reproductive and postmenopausal age was 35 U/ml. Nevertheless, sensitivity of CA125 in the early stage of ovarian cancer was lower. In stage I disease CA125 was elevated by 23-50% [2].

Unfortunately, CA125 is not specific to ovarian cancer and can also be elevated in endometriosis, fibroids or pregnancy, whereas in cirrhosis of the liver it occurs together with ascites. Especially, it is elevated in about 80% of epithelial ovarian cancer cases in advanced stages. The normal range of CA125 was observed in 50% of early-stage cases of ovarian cancer [3]. For better assessment, glycoprotein HE4 (human epididymis protein 4) was introduced [4]. Preoperative assessment of a pelvic mass tumor is highly important to choose the best way of treatment. Zhang et al. reported that the highest level of identification of the tumor is through using a combination of transvaginal ultrasound, color Doppler and serum markers. The sensitivity was calculated as 90.63%, specificity 97.14%. Positive prediction was assessed as 93.94%, negative as 98.55% [5].

Zheng et al. confirmed sensitivity and specificity of CA125 as 64.29% and 53.57% in stage 1 and 2 and 91.43% and 88.57% in stage 3 and 4 of ovarian cancer, respectively. Sensitivity and specificity of HE4 were assessed as 46.4% and 43.3% in stage 1 and 2 and 88.6% and 49.2% in stage 3 and 4 of disease [6]. For differential diagnosis also CA19-9, CEA and estradiol are used. However, there is no specific marker for diagnosis of ovarian cancer.

Progression and treatment of ovarian cancer depend on many factors. Firstly, histological type of disease plays a significant role. The most frequent is the serous one, which in most cases is also correlated with BRCA mutation. The second one is endometrioid type of ovarian cancer and then clear cell type. Both types - endometrioid and clear cell - can be affected by long-term endometriosis. Wentzensen et al. [7] observed in their study a correlation between risk factors and different histological types of ovarian cancer [7]. In every case of ovarian cancer the genetic background should be evaluated. Especially BRCA mutation is often observed. Genetic predisposition for morbidity influences progression of the disease and early onset. New methods of treatment, e.g. PARP inhibitors or immunotherapy, can be used in these cases so it is necessary to know the genetic status of ovarian tumor. The aim of the study was to determine the correlation between the value of markers used in primary diagnosis of ovarian cancer and histological type of cancer and genetic status of patients with ovarian cancer.

Materials and Methods

The study is a preliminary report, where further investigation is needed. Analysis was based on 55 patients from the clinic with diagnosis of ovarian cancer with mean age 60.78±12.99 (median: 63.25 years). Each patient underwent surgical treatment. After the surgical procedure patients were classified according to the FIGO classification from stage IC to IVA [Table 1]. Histological type of ovarian cancer was confirmed after the hematoxylin and eosin staining protocol and immunohistochemistry procedures. Patients were divided into 2 groups. Group A consisted of 36 women with serous type of ovarian cancer with mean age 62.76±12.09 (median: 64.58 years). Group B consisted of 19 women with endometrioid type with mean age 58.13±14.95 (median: 53.8 years). In every case tissue from the ovarian tumor was investigated for BRCA mutation using NGS (next generation sequencing) methods. In all cases adjuvant chemotherapy based on carboplatin and paclitaxel was initiated after surgical treatment.

Table 1: FIGO staging in ovarian, fallopian tube, peritoneal cancer (2014).

I	Tumor confirmed to ovaries or fallopian tubes
IA	Tumor limited to 1 ovary or fallopian tube, capsule intact, no tumor on Surface, negative washings
IB	Tumor involves both ovaries or fallopian tubes (capsule intact), no tumor on Surface of ovaries or fallopian tubes, negative washings/ scites
IC	Tumor limited to 1 or both ovaries or 2 fallopian tubes, with:
IC1	Surgical spill
IC2	Capsule rupture before surgery or tumor on ovarian Surface
IC3	Malignant cells in the ascites or peritoneal washings
II	Tumor involves 1 or both ovaries or fallopian tubes with pelvic extension (below the pelvic brim) or primary peritoneal cancer
IIA	Extension and/or implant on uterus and/or fallopian tubes
IIB	Extension to the other pelvic intraperitoneal tissues
III	Tumor involves 1 or both ovaries and 1 or both fallopian tubes, or primary peritoneal cancer with metastasis to the peritoneum beyond the pelvis and/or positive retroperitoneal lymph nodes
IIIA1	Positive retroperitoneal lymph nodes only (cytologically or histologically confirmed)
IIIA1(i)	Metastasis ≤ 10mm in greatest dimension
IIIA1(ii)	Metastasis > 10mm in greatest dimension
IIIA2	Microscopic extrapelvic peritoneal metastasis (above the pelvic brim) with or without positive retroperitoneal lymph nodes
IIIB	Macroscopic, extrapelvic peritoneal metastasis ≤ 2cm in greatest dimension with or without positive retroperitoneal limph nodes. Includes extension to capsule of liver/spleen without parenchymal infiltration
IIIC	Macroscopic, extrapelvic, peritoneal metastasis > 2cm in greatest dimension with or without positive retroperitoneal limph nodes. Includes extension to capsule of liver/spleen without parenchymal infiltration
IV	Distant metastasis excluding peritoneal metastasis
IVA	Pleural effusion with positive cytology
IVB	Parenchymal metastasis, metastasis to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

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Laboratory Tests

Before the operation laboratory tests were performed. Value of CA125 (normal range: 0-35 U/ml), HE4 (with normal range below 70pmol/L for premenopausal women and 140pmol/L after menopause) were monitored. In every case the ROMA algorithm was used for calculation of the risk of ovarian cancer according to reproductive or postmenopausal age. Higher risk of epithelial ovarian cancer related to ROMA is calculated as more than 25.3% for postmenopausal women and more than 7.4% in reproductive age. Other tests performed in differential diagnosis were: CA19-9 (normal range: 0-37 U/ml), CEA (0-5ng/ml) and estradiol (normal range in correlation to menstrual cycle). After 6 courses of chemotherapy the value of CA125 was assessed to monitor the effectiveness of treatment.

Statistical Methods

To test significant differences between groups, Student's t-test and the Mann-Whitney test were used. P<0.05 was considered to indicate a statistically significant difference. Also the chi-square test was used due to compare two features.

Results

Value of CA125

The level of CA125 was compared before the surgical procedure and after 6 courses of chemotherapy based on paclitaxel and carboplatin. In group A the mean value of CA125 was 1705.94±2468.67 IU/ml (median 380.5), and HE4 was 532.08±815.74 (median 127). After calculation the range of ROMA algorithm was calculated as 70.03%±31.66 (median 82.59%). The mean value of CA125 after chemotherapy decreased to 159.22±336.42 IU/ml (median 19.5). In group B mean value of CA125 was 364±699.18 (median 46), HE4 183.74±326.88 (median 56) .ROMA score was 42.16%±30.78 (median 25.6%). Mean value of CA125 after chemotherapy was 12.28±6.88 (median 10).

The level of CA125 at the time of diagnosis was statistically significant for serous (p=0.006) and endometrioid (p=0.01) type of ovarian cancer. Statistical significance of level of HE4 was observed in serous ovarian cancer (p = 0.021) [Figure 1].

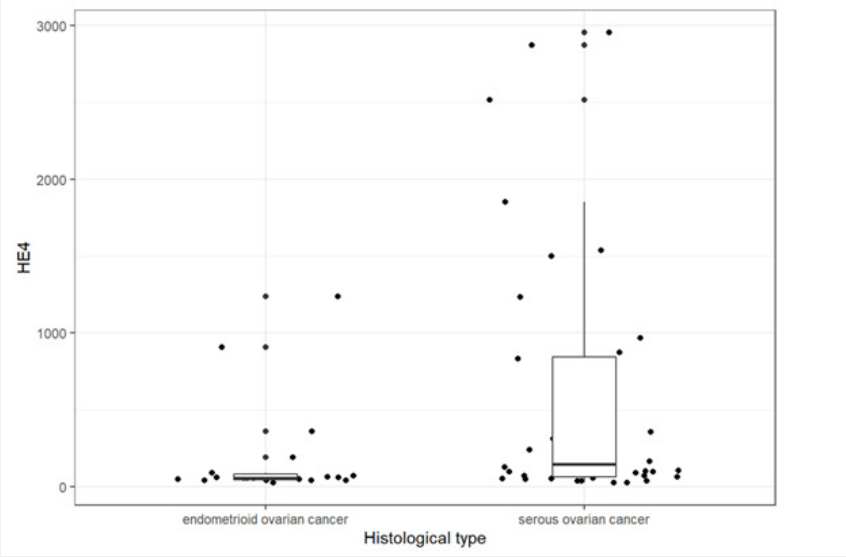

Figure 1: Correlation of HE4 and histological type of ovarian cancer.

There was a significant correlation between the calculated value of the ROMA algorithm and serous type of ovarian cancer (p=0.02) [Figure 2].

Statistical analysis revealed a higher value of CA125 after chemotherapy in serous type of ovarian cancer in comparison with endometrioid ovarian cancer. A decreasing level of CA125 was correlated with histological type (p<0.05) [Figure 3].

Value of Other Markers

Ca19-9 was in the normal range in 91.7% of group A and 89.5% of group B. In group A in 5.5% the level of CEA was increased. Otherwise, all women from group B were in the normal range of CEA. The correct value of estradiol was confirmed in all patients. There was no statistical correlation with histological type of ovarian cancer.

Genetic Tests

Presence of BRCA mutation in ovarian tumor was confirmed in 8.3% of group A and 15.8% of group B. Mean age of patients with serous type of ovarian cancer and BRCA mutation was 62.26±10.52 (median 64.31 years). Mean age of women with endometrioid type and BRCA positive was 46.79±3.35 (median 48.19 years).

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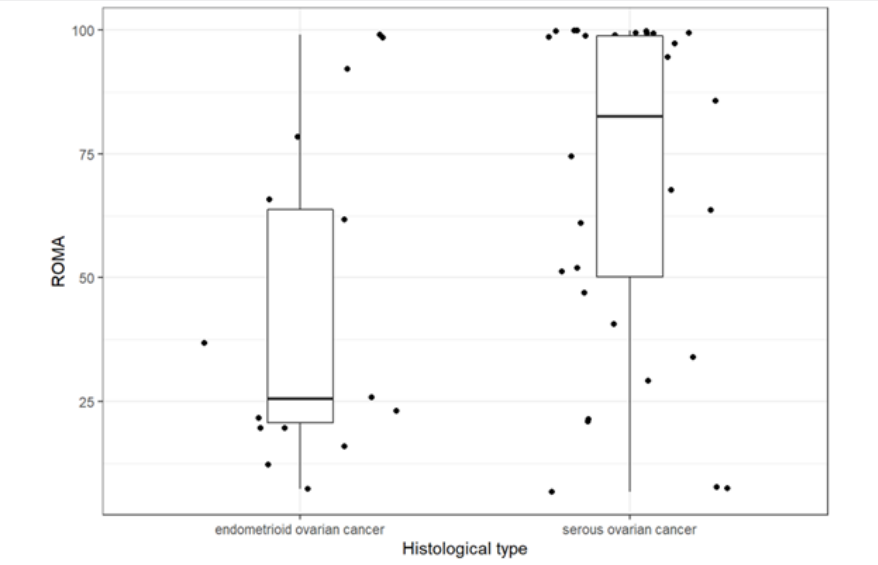

Figure 2: Correlation of ROMA and histological type of ovarian cancer.

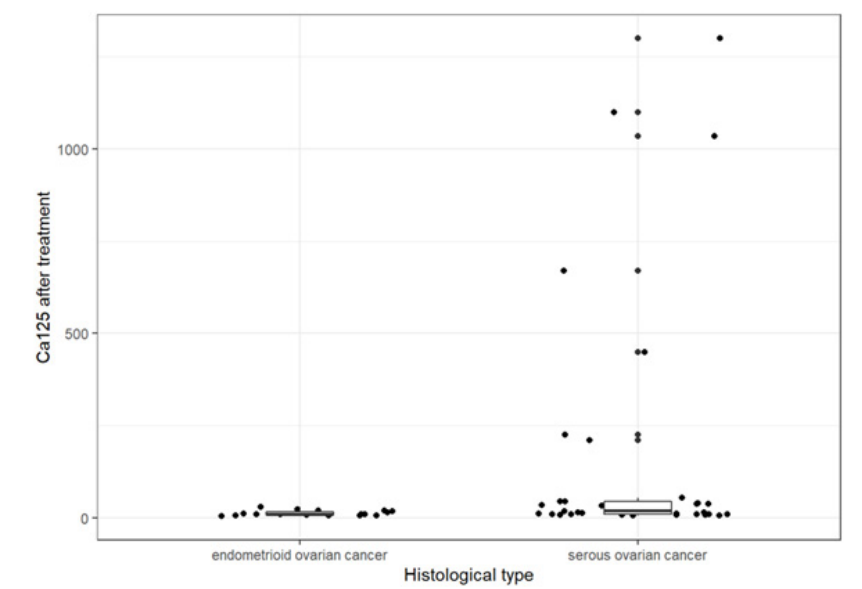

Figure 3: Correlation of CA125 after treatment and histological type of ovarian cancer.

There was no correlation of presence of BRCA mutation and histological type of ovarian cancer. No significant correlation was observed between presence of BRCA mutation and value of CA125 before the surgical procedure and after chemotherapy. The lack of statistical significance may be due to the small population size.

Discussion

Early diagnosis of ovarian cancer allows for quicker implementation of treatment. Extensive analysis performed in the United States of America revealed a correlation between histological types and effects on treatment and longer survival. Higher mortality is observed in carcinosarcoma. The most common ovarian cancers are high-grade serous type and endometrioid. As they are so frequent, they have been the target of many investigations [8].

In retrospective analysis in China sensitivity and specificity in suspicion of ovarian cancer were assessed as 93.2% and 87.5% [9]. Probability of malignancy is significant in preoperative assessment and qualification for treatment. Ferraro et al. assessed specificity of CA125 as 78% [10]. Grandi et al. [11] revealed CA125

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in 1st stage ovarian cancer in 54.4%, which increased in the second stage to 78%. Higher specificity is observed in endometrioid type of ovarian cancer.

May et al. observed prognostic value of CA125 in high-grade serous ovarian cancer. The cut off value was defined as 174U/ml. Comparison of the preoperative and postoperative value of CA125 revealed a decreasing concentration of this marker [12]. Lee et al. [13] reported a correlation between lower value of CA125 after chemotherapy and longer overall survival in advanced ovarian cancer. In our analysis concentration of CA125 also decreased after the surgical procedure and then after 6 courses of chemotherapy. Moreover, in our research, a higher level of CA125 was observed in the serous type of ovarian cancer than in the endometrioid one.

The prognostic role of CA125 before and after treatment was investigated by Fadera et al. [14] In the first stage of ovarian cancer CA125 before treatment was not prognostic and had no influence on overall survival. However, during treatment the value of CA125 is normalized. The value of CA125 before the second line chemotherapy has an influence on decreasing risk of death because of ovarian cancer.

Shen et al. published a study with superior sensitivity of HE4 than CA125 in predicting the surgical outcome of primary debulking surgery and interval debulking surgery. They claimed that the change of HE4 during neoadjuvant chemotherapy could predict the outcome of interval debulking surgery [15]. Similarly, Steffensen et al. [16] revealed HE4 as a strong indicator of epithelial ovarian cancer. They observed a correlation between higher concentration of HE4 and worse prognosis of disease. According to our investigation, HE4 is statistically correlated with serous type of ovarian cancer. Further studies are necessary for better usage of this indicator.

The ROMA algorithm was created for better preoperative prediction of ovarian cancer according to presence of ovarian tumor. Calculation is correlated with reproductive or postmenopausal age. Sensitivity and specificity of ROMA for reproductive age were reported as 0.714 and 0.972, for postmenopausal age as 0.929 and 0.8. Nevertheless, no correlation was found according to histological type of ovarian cancer and stage of disease [17]. Simmons et al. [18] observed a positive role of the markers CA125, HE4, MMP-7 and CA 72-4 in early detection of ovarian cancer. We detected in our investigation a statistical significant correlation between the value of CA125 and serous and endometrial type of ovarian cancer.

The marker CA19-9 and its role in diagnosis of ovarian cancer were described by Zhang et al. [19] The aim of that study was to determine contrast enhanced ultrasound with CA19-9/CA125 to differentiate ovarian serous carcinoma from ovarian malignant epithelial cancer. Concentrations of CA19-9 and CA125 were significantly higher in ovarian malignant epithelial cancer. In our research no statistical significance of use of CA19-9 in ovarian cancer diagnosis was found.

Koshiyama et al. [20] described differential diagnosis of histological types of ovarian cancer according to classification of type I (endometrioid, clear cell, mucinous, low-grade serous) and II (high-grade serous). Presence of BRCA mutation was higher in II type ovarian cancer. In our analysis due to the smaller population estimation of gene mutation was not statistically significant.

Frequency of BRCA mutation was described by Zhang et al. [21] in analysis based on 1342 women. They confirmed coexistence of serous type of ovarian cancer and BRCA positive mutation in 18% of cases. No mutation was seen in mucinous carcinoma. Due to the smaller population, the percentage of positive BRCA mutation was lower. Kim et al. in their investigation found a correlation with positive BRCA mutation and longer overall survival in comparison to patients with no genetic background [22].

On the other hand, Zheng et al. [23] conducted a study on familial risk of ovarian cancer. Early morbidity connected with familial background was observed especially in endometrioid and serous types of ovarian cancer. Raspollini et al. [24] reported correlations of CA125 and COX-2 with survival and clinical responsiveness to chemotherapy in ovarian cancer. Level of CA125 before onset of treatment was significant. Further investigations are necessary to better understanding the role of COX-2 in the pathomechanism of ovarian cancer.

Conclusion

Laboratory tests used in clinical practice for diagnosis of ovarian cancer are not sufficiently specific to differentiate histological types of disease. However, CA125 has a significant role in monitoring effectiveness after chemotherapy, which is correlated with histological type of tumor. Presence of BRCA mutation is a risk factor of morbidity of ovarian cancer and is not linked to only one histological type. Further investigations on a larger population are needed. Our investigation is an introduction to a long-term project. This preliminary report exposes the problem of lack of specific and sensitive methods to differentiate ovarian cancer and its histological types. In the future we are planning to publish a longer report based on our observations.

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