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Evaluation of risk factors and effective factors in determining the prognosis of ovarian cancer

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ABSTRACT

Ovarian cancer is still one of the leading causes of death from reproductive system cancers. Despite recent advances in treating this cancer, ovarian cancer is the fourth cause of death in women. Knowing the risk factors of ovarian cancer and the factors affecting the prognosis of this tumor can be helpful. This study investigates risk factors and practical factors in determining the prognosis of ovarian cancer. In the present study, we searched through various databases such as Wiley Online Library, Google Scholar, PubMed, and Elsevier with the keywords Polycystic Ovarian, Ovarian Estrogen-Dependent Tumors Syndrome Chronic Inflammation, Prognosis of Ovarian Cancer, among published articles from 1996 to 2022. Based on these studies, we investigated the age of menstruation, age of menopause, number of pregnancies, family history of ovarian cancer and genital tract cancer, use of birth control pills, histological type of tumor, degree of cell differentiation, type of surgery, and post-surgery treatments, and examination of the serum level of tumor marker CA12, as well as the role of polycystic ovary syndrome in the development of ovarian cancer. In general, infertility was one of the most important risk factors and the serum level of tumor marker CA125 was one of the most important determinants of ovarian cancer prognosis.

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Introduction

Investigation of the causes of women's death has shown that cancers are the second cause of death among women, and ovarian cancer is the fourth cause of women's death among cancers of the reproductive system (1). Although, despite the improvement of ovarian cancer treatment methods in the last decade in the world, the life expectancy of patients has increased. Finally, in the long term, the life expectancy of patients has increased slightly (2). Despite proper treatment, one of the main reasons for mortality in these patients is the late presentation of women with ovarian cancer, especially epithelial group tumors (3). Therefore, to prevent the disease's risk factors and recognize the patients' clinical symptoms, efforts should be made to reduce the prevalence of the disease and its consequences. Especially in modern healthcare, primary prevention is the preferred method compared to other cases (4). Examining the influential factors in determining the prognosis of ovarian cancer in the direction of early recognition of disease recurrence will be helpful. Although, in the long run, the life expectancy of the patients will not change much, their quality of life will improve anyway (3, 5).

Several studies have investigated risk factors and determined practical aspects of ovarian cancer prognosis (4, 6). One of them is the study done in Beijing, China (7), which showed that the prognosis of ovarian cancer patients has improved due to the advancement of treatment methods. Another study that was done in 1998 mentioned the relationship between birth control pills as a preventive factor and a family history of ovarian cancer as a risk factor for this disease (8). Another study was conducted in 2020 on the factors influencing the prognosis of ovarian cancer and showed that increasing age has the opposite effect on the prediction of ovarian cancer (9). This study was conducted to identify the risk factors and practical factors in the prognosis of ovarian cancer.

Materials and Methods

In the present study, we searched through various databases such as Wiley Online Library, Google Scholar, PubMed, and Elsevier with the keywords Polycystic Ovarian, Ovarian Estrogen-Dependent Tumors Syndrome Chronic Inflammation, Prognosis of Ovarian Cancer, among published articles from 1996 to 2022.

Results

Ovarian cancer and demographic information

Ovarian cancer is the fourth leading cause of fatal malignancies in developed countries and the most common cause of death among cancers of the reproductive system (10). Ovarian epithelial cell tumors are responsible for 90% of ovarian malignancies (11). Despite identifying new treatment methods for ovarian cancer, most patients relapse after initial treatment due to late diagnosis, especially when the venom is very advanced (12). Studies have shown that diagnosing the disease can reduce the probability of death from this cancer by 50% (13). Meanwhile, only 19% of ovarian malignancies can be interpreted in the early stages (4, 12). Therefore, it is essential to know the

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risk factors of ovarian cancer to diagnose this disease early and ultimately reduce the mortality caused by it. Several factors are the underlying cause of ovarian cancer (14). Among them, we can mention demographic information such as age, menstruation age, weight, race and nationality have been considered suspected factors in increasing the risk of this cancer (12).

The relationship between the patients' average age and pathology classification showed that the average age in the group of epithelial tumors was 49.7 years, and in the group of germ tuberculosis tumors, 23.6 years (14). Considering different articles, the age group of genital tumors was evaluated at about 35.5 years. In the group of metastatic tumors, it was 42 years (15). The highest average age in the group of endometrioid tumors was 65 years, and the lowest average age in embryonal carcinoma tumors was 16 years (15, 16). The study of recorded cases showed that the average age of menarche in the epithelial tumors group was 15 years and in the genital cord tumors group was 13 years. In 13.8% of the cases, the same age was not specified. The relationship between the average weight of the patients and the type of tumor histology showed that the highest average weight was 62 kg in the endometrioid tumor type, and the lowest weight was seen in the embryonal carcinoma group, which was 36.2 kg (12). Ovarian cancer is the fifth most commonly diagnosed cancer among women in the U.S. Similar to breast and endometrial cancers. Ovarian cancer is more common among women in northern and central Europe and in North America compared with Africa, South America, and Asia. In the U.S., substantial racial and ethnic variations have been observed in the incidence of ovarian cancer (17). This analysis substantiates a higher risk of ovarian cancer among white women and women who are not Hispanic than among black, American Indian, Asian/Pacific Islander, and Hispanic women (16, 17).

Different stages of ovarian cancer

The condition of cancer patients is different and depends on factors such as how the tumor develops and progresses, the extent of lymph node involvement, and metastasis to distant tissues and organs. Determining the cancer stage helps the doctor make treatment decisions (12). Ovarian cancer has four stages, each of which is divided into other sections, as presented in Table 1.

The four stages presented in Table 1 create different states for patients according to the TNM system (5), shown in Table 2.

It should be noted that N is the beginning of the word Node. N0 means that the lymph nodes are not involved in cancer cells. N1 means that the lymph nodes are involved with cancer cells (8). According to the grade (low grade and high grade) and the tumor stage, the duration of doubling the tumor size (growth and proliferation of cancer cells) will be different (17). Therefore, in addition to determining the state of the tumor as an input to the model, the grading and staging of the tumor must also be known. Different grades of ovarian tumors in various references are low-grade and high-grade (14). Low grade is related to early-stage statuses 1 to 5, presented in table 2, and High-grade grading pertains to advanced-stage statuses 6

Table 1. Different stages of ovarian cancer.

Stage I	
Cancer is confined to one ovary (tumor confined to one ovary).	IA
The cancer is located in two ovaries (the tumor is limited to both ovaries).	IB
The tumor is present in one or both ovaries and also on the surface of one ovary.	IC
Stage II	
Development of cancer to fallopian tubes or uterus	IIA
Development of cancer to pelvic tissue	IIB
Stage III	
Lymph nodes smaller than or equal to one centimeter are involved in cancer cells (N1a).	IIIA1(i)
The lymph nodes are more than one centimeter involved in cancer cells (N1b).	IIIA1(ii)
The cancer is located in one or both ovaries or fallopian tubes and has spread to the peritoneum outside the pelvis (above the pelvic brim). The lymph nodes (retroperitoneal) may or may not be involved with cancer cells (N1/N0).	IIIA2
The tumor is present in one or both ovaries and has spread to the abdomen (peritoneum) (macroscopic peritoneal metastasis beyond the pelvis, up to 2 cm in largest dimension). With or without metastases to the retroperitoneal lymph nodes	IIIB
The tumor has spread to the abdomen (peritoneum) (macroscopic peritoneal metastases beyond the pelvis more than 2 cm in most significant dimension), and surface metastases to the liver or spleen may also occur (but not into the liver or spleen). Inguinal lymph nodes or retroperitoneal lymph nodes may or may not be involved with cancer cells (N0/N1).	IIIC
Stage IV	
In addition to being present in the ovary and having any (limited) spread, cancer has also caused fluid in the lung (pleural effusion with positive cytology).	IVA
In addition to being present in the ovary, cancer can spread to any extent (any T) to the liver, spleen, and lymph (Lymph nodes include N0, N1, and N2 states)(metastasis to extra-abdominal organs).	IVB

to 16, shown in table 2 (3). In other words, patients in the early stage have a low grade, and patients in the advanced stage have a high grade. The ability to grow and expand the tumor was included in the model's development according to the tumor's staging and grading and Table 3 (16). Therefore, the ovarian cancer conditions in Table 2 can be seen in the tumor selection and growth and expansion model (3).

Table 2. Different states of ovarian cancer.

State Number	State Name
1	T1aN0M0
2	T1bN0M0
3	T1cN0M0
4	T2aN0M0
5	T2bN0M0
6	T1N1aM0
7	T1N1bM0
8	T2N1aM0
9	T2N1bM0
10	T3a2N0M0
11	T3a2N1M0
12	T3bN0M0
13	T3cN0M0
14	T3cN1M0
15	Any T, Any N, M1a
16	Any T, Any N, M1b

Table 3. The average time of doubling the size of the tumor (in days) according to the staging and grading of the tumor.

Tumor Staging	Tumor Doubling Time
Early Stage	Almost every four months (120 days)
Advanced Stage	Almost every two and a half months (75 days)

The grading of cell differentiation and the disease stage

Examining the grade of tumor cellular differentiation in different studies showed that, generally, the highest frequency of cellular differentiation was observed in grade 2 and the lowest in grade 1. For example, in the study by Kerio et al. (5), the frequency of grade 1 was 23.4% and the lowest. The frequency of grades 2 and 3 was 38.3% and 37.9%, respectively. In the group of epithelial tumors, the most common frequency of cell differentiation was grade two (6.53%), and the rarest frequency was grade one (6.3%). In the group of germ cell tumors, the most cases were tumors in grade one disease (7.72%), and in the group of genital cord tumors, 50% of cases were in grade 2 and in the category of metastatic tumors, the most cell grade was grade two.

On the other hand, the most common stage of the disease was Stage IIIc, and the rest of the patients were between Stage Ia and Stage IVa of ovarian cancer. For example, in a study by Zoure et al. (18), 23.4% of patients were in stage 3. In this study, patients with ovarian cancer were all subjected to surgery, which could be different from a simple sampling (biopsy) to complete surgery and removal of tumoral cells as much as possible, i.e., surgery to reduce the volume of cells. Unilateral ovarian tumor removal was performed in 11% of cases, bilateral tumor removal was performed in 2.7% of cases, and cell volume reduction surgery was performed in 58% of cases. Tumor staging during surgery was performed in 49% of patients, and cell volume reduction surgery and tumor staging were performed in 41.5% of patients. In 46% of the cases, the surgery was performed optimally; that is, the remaining tissue from the tumor was not removed, or its size was less than one centimeter, and in 54% of the cases, the surgery was performed less than optimally. Post-surgery treatments included chemotherapy, which varied from one to thirteen courses. But the most common method was four and six rounds, which were performed in 29.8% and 37.8% of patients (17). The most frequent chemotherapy regimen used in patients with epithelial tumors was cisplatin, cyclophosphamide (PC) regimen, which constituted 37.3% of cases, and bleomycin etoposide and cisplatin (BEP) regimen was the second most commonly used regimen in patients, especially in the group of tumors. Tuberculosis was 17.3%. 19.6% of patients underwent radiation therapy due to a lack of response to chemotherapy and inability to re-surgery (19).

Ovarian cancer and Polycystic Ovarian Syndrome (PCOS)

Gonadotropins, estrogens, and androgens stimulate the proliferation of malignant human ovarian epithelial cells and healthy cells in vitro (20, 21). In addition to promoting cell proliferation, estrogen may play a role in ovarian tumorigenesis by inhibiting apoptosis and increasing the amount of B-cell lymphoma 2 (Bcl2)(22). In contrast, progesterone exerts its pro-apoptotic effects on ovarian epithelial cells by regulating the expression of Bcl-6. Transforming Growth Factor Beta (TGF-β) activates the signaling pathway of the FAS molecule and Fas/FasLigand (23). Androgens may also promote ovarian cancer by reducing the level of the TGF-β receptor, thus allowing tumor cells to escape from growth inhibitors through TGF-β1 is given (24). Figure 1 shows the TGF-β-induced fibrosis signaling pathway (25).

Also, the continuous use of ovulation-inducing drugs to treat infertility caused by PCOS plays a vital role in developing ovarian tumors (26). On the other hand, the loss of ovarian surface epithelial cells in retention cysts increase the risk of becoming malignancy due to the contact of these cells with androgen-rich hormonal stroma (21, 26). Obesity associated with PCOS is also a significant risk factor for various cancers, including ovarian cancer. There is conflicting evidence regarding the relationship between PCOS and the risk of ovarian cancer (21). Most

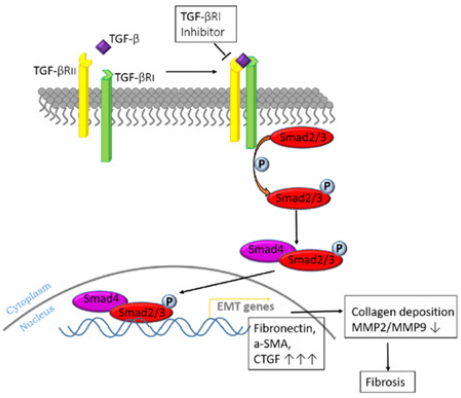

Figure 1. DHEA-induced ovarian hyperfibrosis is mediated by TGF-β signaling pathway (25).

researchers cite a study to prove this hypothesis published by Schildkraut et al. (27). This study showed a 2.5-fold increased risk of ovarian cancer (95% CI: 1.1-5.9) among women with PCOS. In addition to studying the prevalence of cancer in PCOS women, Schildkraut et al. (27) have also investigated and studied the effect of Oral Contraception Pills (OCP) on the occurrence of ovarian malignancy. This study also showed that women with PCOS who did not take OCP pills for at least three months had an increased risk of ovarian cancer (Odd Ratio [OR]: 10.5, 95% CI: 2.5-44.2). While, women who had used OCP for the same period faced a much lower risk (OR: 1.1, 95% CI: 3.0-4.7) for the same period. These findings point to the possible role of OCP pills in protecting women with PCOS and suffering from ovulation disorders against ovarian cancer. The mechanism is through the suppression of gonadotropins that prevent continuous ovulation, which is an obvious risk. It prevents the formation of retention cysts, epithelial proliferation, genetic damage, and ovarian malignancy (28). So far, several studies have reported an increased risk of ovarian cancer due to the use of clomiphene (an ovulation-stimulating drug), which is prescribed to treat infertility caused by PCOS in women with fertility disorders; in one of these studies, an increase of 2.3 times (OR: 2.3, 95% CI: 0.5-11.4) was observed in the population of 3837 women. The results of these investigations also showed that the period of use of this drug could also be related to the increased risk of ovarian cancer in both groups of women with abnormal ovaries or without any malignancy (29). However, in the study of using this drug for less than one year, such a significant relationship was not proven. Many studies have also been designed and conducted to find a connection between the use of antidiabetic drugs, including metformin (for example, in treating insulin resistance caused by PCOS) and the risk of ovarian cancer (30). Figure 2 shows a schematic of possible mechanisms involving hyperinsulinemia, insulin-like growth factor-I (IGF-I), and IGF-binding protein-1 (IGFBP-1) in premature adrenarche and polycystic ovary syndrome (PCOS)(31).

Meanwhile, the investigation of the long-term use of metformin in the population of 1611 people with ovarian cancer and the control group showed a decrease in the risk of ovarian cancer (OR: 2.29, 95% CI: 1.13-4.65) (32). Also, Gotlieb et al. (33) and Rattan et al. (34) also reported that a high concentration of metformin stops the growth of cancer cells and enhances the cytotoxic effects induced by cisplatin (Cisplatin, a cytotoxic drug used in cancer chemotherapy). Ratan's study also suggested that metformin is an inducer of AMP-Activated Protein Kinase (AMPK) activity, which is the primary activator in the cellular response to a low concentration of ATP, and by suppressing the mTOR signaling pathway; it is effective in inhibiting the growth of ovarian cancer cells. However, more studies are needed in this field due to the prevalence of at least 3% of ovarian cancer among women with PCOS. A significant relationship between PCOS and the risk of ovarian cancer has not yet been confirmed. Several studies conducted in this field have rejected the existence of such a relationship. For example, in a cross-sectional survey conducted by Atiomo et al. (35) on 217 people with PCOS (compared to healthy people) in England, no positive association was found between PCOS and a family history of ovarian cancer. Also, in a case-control study in Australia to prove they investigated the hypothesis of the effect of androgens on ovarian epithelial cell cancer, 1276 cases of invasive epithelial ovarian cancer, 315 cases of ovarian tumors with undetermined malignant severity and cases without a definite diagnosis (36). The results of this study also did not report any positive relationship between acne or hairy PCOS with all invasive cancers and only a weak relationship between the history of PCOS or hairy and borderline ovarian tumor (OR: 1.8, 95% CI: 0.9-2.3 and OR: 1.5, 95% CI: 0.8-3.9) showed. The results of a large cohort study conducted over 35 years to 2014 on 12,070 patients with PCOS reported 279 cases of cancer among women with PCOS (37). Still, there was a significant relationship between this disease and breast cancers (Standardized Incidence Ratio (SIR): 1.1, 95% CI: 0.8-14) and ovary (SIR: 1.8, 95% CI: 0.8-3.2) was not found, and only a solid significant association with Endometrial cancer (SIR: 3.9, 95% CI: 2.2-6.3) was observed (9).

Ovarian cancer and CA125 tumor marker

CA125 tumor marker has high sensitivity and specificity for ovarian cancer, like AFP and human chorionic gonadotropin (HCG), which are accurate tumor markers for ovarian germ cell tumors. CA125 is a very accurate indicator for ovarian non-mucinous epithelial tumors, and this tumor marker in more than 80% of women with ovarian cancer increases (38, 39). CA125 test is most commonly used to check early signs of ovarian cancer in high-risk women for this disease. But since the level of CA125 increases in many complications and non-cancerous diseases, the CA125 test is not accurate enough to screen for ovarian cancer in all women (40). Also, an increase in CA125 level is observed in many conditions and complications such as menstruation and non-cancerous cases such as uterine fibroids (41).

However, on the other hand, some cancers, including ovarian, endometrial, peritoneal, and fallopian tube cancers, are among the causes of high CA 125. This test cannot be used alone to diagnose ovarian cancer, but it helps to confirm it (42).

In general, several studies showed that the examination of CA125 tumor marker values of epithelial tumors

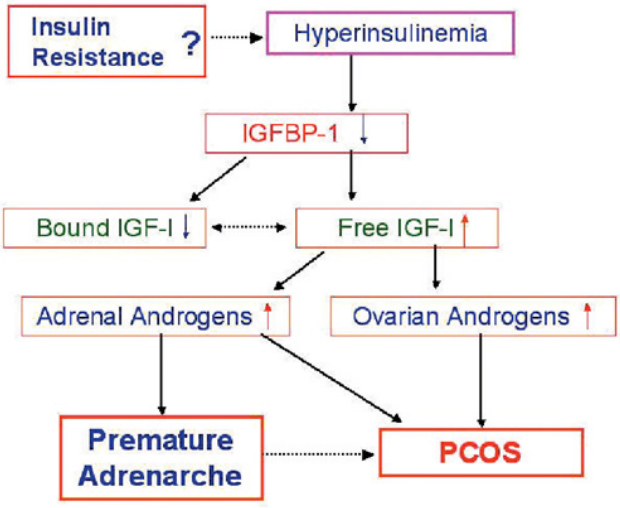

Figure 2. Possible mechanisms involving hyperinsulinemia, insulin-like growth factor-I (IGF-I), and IGF-binding protein-1 (IGFBP-1) in premature adrenarche and polycystic ovary syndrome (PCOS)(31).

in cases of cancer recurrence showed a significant relationship between the rate of disease recurrence and the serum level of the CA125 tumor marker (38, 42, 43). CA125 marker values were significantly higher in cases of pelvic recurrence than in other cases. The examination of the condition of all patients in the last follow-up showed that 66.3 patients were in good condition, 3.09% were in bad condition, 5.3% were in an uncertain situation, and 2.8% of the patients had died (40). The CA125 tumor marker values were measured in all ovarian tumor types, the highest CA125 values were found in the germ cell tumor group, and the lowest value was found in the sex cord tumor group. There was a significant relationship between disease recurrence and the average level of CA125 tumor marker before treatment (39). The average level of CA125 tumor marker in cases of recurrence in the epithelial tumors group was 340.4 units per milliliter, and in patients without recurrence, it was 77.5 units per milliliter (44).

Discussion

Ovarian cancer is the most important cause of death in women due to cancers of the reproductive system (2). According to the American Cancer Society report, 23,400 new cases of ovarian cancer are added annually, and 3,900 patients of ovarian cancer sufferers die yearly (45). Among the risk factors of ovarian cancer, early onset of menstruation and delay in menopause, history of infertility, and use of ovulation-stimulating drugs can be mentioned (46). In the present study, only a positive relationship between infertility and ovarian cancer was seen (11%). Taking birth control pills is one of the protective factors for patients against ovarian cancer. In our study, the opposite was true, and 77.8% of ovarian cancer patients had a history of taking birth control pills. Positive family history of cancer, especially ovarian, uterine and intestinal cancer, and genetic mutation in patients with ovarian cancer have been reported in this review in 3.7% of cases (47). Considering that obesity is not unrelated to ovarian cancer, this issue was investigated. The average weight of the patients in the ovarian epithelial tumor group was the highest in the endometrioid subgroup. But in the group of germ cell tumors and embryonal subgroup, it was the least amount (48).

Considering the prevalence of embryonic cancer at young ages, the lower weight of these patients seems logical (49). However, in terms of factors determining the prognosis of ovarian cancer, it is necessary to pay attention to the fact that ovarian cancer has a broad spectrum in terms of biological behavior, which varies from a good prognosis and the possibility of recovery to a severe and fatal prognosis for patients (2). The reason for this discrepancy is the existence of a series of variables that determine the prognosis of ovarian cancer, among which we can mention the histological features of the tumor, the degree of cell differentiation, and the stage of the disease. Epithelial tumors, obvious cell tumors, have a worse prognosis (38). In the group of epithelial tumors in 67.3% of cases, disease recurrence was seen in recently examined patients, which was more than in the other groups. Similar to other cancers, the higher the degree of cellular differentiation and the stage of the disease, the worse the prognosis will be. Unfortunately, staging and grading were not done in all patients. Although in recent years, most of the surgeons and pathologists of our centers have paid more attention to this matter, naturally, it will be very effective in making treatment decisions (50). The present study showed that in tumors of the ovarian epithelial group, cell differentiation in grade one has the lowest prevalence (3.6%), and in germ cell group tumors, grade one has the most type of cell differentiation (72.7%). Cell volume reduction surgery is the first step in treating cancer patients (51).

The ovary must be removed as much tumoral tissue as possible, and the amount of remaining tissue should reach its minimum (13). Studies have shown that in the last two decades, due to more surgery to reduce the volume of cells and chemotherapy, the prognosis of patients with ovarian cancer has become relatively better, even in the advanced stages of the disease (52). In our study, surgery to reduce the cell volume was performed more, especially in the last years of the study, and among these cases, the desired surgery was performed in 54% of the patients (5). In cases with unacceptable medical conditions for surgery or the patient has ascites, chemotherapy is recommended before surgery. In our study, this was only done in a few cases, which was not statistically significant. Although the volume of the primary tumor is not the only factor that determines the prognosis of patients with ovarian cancer, it seems that the volume of the remaining tumor has an inverse relationship with the patient's life span. In our study, post-epithelial tumors of the germ cell category had the most tumor volume after surgery, and recurrence was higher in this group than in other tumors (52). The next issue that should be mentioned is that in the literature review, increasing age has been mentioned as a factor determining the prognosis of ovarian cancer, which is because patients are referred in the advanced stages of the disease and the presence of specific underlying diseases. In a recent study, the average age of ovarian epithelial tumors in the case of disease recurrence was 46 ± 17.7 years, and in people without recurrence, it was 38 ± 17.1 years (53).

The next issue mentioned in several studies is the correlation of tumor marker CA125 with the prognosis of ovarian cancer (51). The serum level of tumor marker CA125 before surgery has been cited as an independent factor determining the prognosis of patients with ovarian cancer (54). Although the level of the CA125 marker has a direct relationship with the staging of the disease and the amount of residual tissue after surgery, as well as predicting the response of the tumor to chemotherapy, it cannot be considered an ideal predictive factor and still needs more studies in this field (55). In our research, the CA125 tumor marker was not measured before surgery in all patients (8). In most cases of epithelial tumors, the level of this tumor marker after surgery was considered the primary criterion. But in any case, there was a significant positive relationship between the rate of disease recurrence and the serum level of tumor marker CA125 (55). Also, there was a positive relationship between the site of repetition and the amount of this tumor marker. The highest amount of this tumor marker was seen in cases of pelvic recurrence (1295 units per milliliter), among other things that play a role in determining the prognosis of ovarian cancer. The increase of interleukin-6, CRP, and βhCG values can be mentioned, which were not measured in our study. In recent years, much attention has been paid to studying genetic and immunological factors, such as the increase in HER/2 and GC-myc gene expression, tumor aneuploidy, and the increase in plasminogen activator fac-

tor (13). Also, the growth of the insulin-like activating factor bikunin has been indicated for evaluating the prognosis of ovarian cancer (56).

Finally, we can conclude that infertility is one of ovarian cancer's most critical risk factors. Also, cases of epithelial ovarian cancer with an increase in CA125 serum level are more prone to disease recurrence, so it is recommended to follow up with these people with more careful and accurate cut-off intervals.

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