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OVARIAN CANCER

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Abstract

Ovarian cancer is the seventh most commonly diagnosed cancer among females and the most lethal gynaecologic malignancy globally because of its vague presentation, insidious nature, recurrence, and drug resistance. There is a pressing need to improve survival and quality of life in patients with ovarian cancer in the context of rising global incidence, high risk of relapse, and poor prognosis. Presentations at the European Society for Medical Oncology (ESMO) Congress 2022 from 9th–13th September in Paris, France, showed the breadth and depth of research in ovarian cancer, including a first look at the highly anticipated data from Phase III studies on the impact on overall survival (OS) of poly(ADP-ribose) polymerase (PARP) inhibitors as first-line maintenance therapy. Clinically meaningful OS benefit was shown with olaparib at 5 years' follow-up in PAOLA-1 and at 7 years' follow-up in SOLO1.

Keywords: Ovarian cancer, epidemiology, risk factor

INTRODUCTION

Ovarian cancer is the leading cause of death in women diagnosed with gynecological cancers. It is also the fifth most frequent cause of death in women, in general. Most of the cases are diagnosed at an advanced stage, which leads to poor outcomes of this disease. The existing screening tests have a low predictive value contributing further to this misery. Detailed gyn ecological evaluation along with transvaginal ultrasound and laboratory marker like cancer antigen-125 (CA-125) assay are the key early detection strategies which have shown no significant beneficial effect in the morbidity or mortality of this cancer. LIke many cancers, the incidence of ovarian cancer varies across the world. The epidemiological diversity of ovarian cancer in different regions can be attributed to the risk factors that account for the occurrence of ovarian cancer. The highest prevalence of ovarian cancer is seen in non-Hispanic white women (12.0 per 100,000), followed by Hispanic (10.3 per 100,000), non- Hispanic black (9.4 per 100,000), and Asian/Pacific Islander women (9.2 per 100,000). However, due to differences in access to diagnostic and therapeutic services, the mortality of ovarian cancer has a different pattern, and the highest mortality rate is seen in African populations. The statistics show that between one third to two fifths of the total cancer cases can be prevented by eliminating and reducing risk factors. Considering the fact that knowledge on the incidence, mortality, and geographical diversity of ovarian cancer as well as its risk factors is necessary for planning and preventing complications, and since we could find no comprehensive study on the risk factors of ovarian cancer in the world, the aim of this study was to examine the trends in incidence and mortality across the world and to present all possible factors associated with OC.[(1)]

Etiology

There are various risk factors associated with ovarian cancer. It mostly affects postmenopausal women, where increasing age is associated with an increased incidence, advanced stage of this disease, and lower reported survival rates. Parity poses a protective role according to a few case-control studies with higher age at childbirth linked to a decreased risk of ovarian cancer. The strongest risk factor of ovarian cancer is a positive family history of breast or ovarian cancer, where a personal history of breast cancer also augments the risk. Several studies have shown an increased risk of smoking, especially the risk of mucinous epithelial tumours. In 2020, there are approximately 21,750 new ovarian cancer cases, which comprises 1.2% of all cancer cases. The estimated number of deaths related to it are 13,940. The 5-year relative survival rate is expected to be 48.6%. Around 15.7% of the ovarian cancer cases are diagnosed at the local stage, and about 58% at the metastasized stage, where the 5-year survival dips down to 30.2% instead of 92.6% if detected at an early stage of local spread. An average incidence rate per 100,000, age-adjusted to the 2000 US standard population is 11.1 in 2012-2016. The incidence is highest in non-Hispanic whites (11.6 per 100,000), followed by American Indians and Alaska Natives (10.3 per 100,000), Hispanics (10.1 per 00,000), non-Hispanic blacks, and Asian and Pacific Islanders. Ninety percent of ovarian cancers are epithelial, with the serous subtype being the most common. Age-adjusted rates of new ovarian cancer cases are on a reducing trend based on statistical models of analysis.[2]

Pathogenesis of Ovarian Cancer

To date, no widely accepted pathogenesis of ovarian cancer has been described. One of the biggest problems in uncovering the pathogenesis of ovarian cancer is the heterogeneous nature of ovarian cancer, comprising various histologic types with different behaviours and characteristics. Although 40% of ovarian tumors are nonepithelial types, only 10% of ovarian cancers are nonepithelial

Incessant Ovulation Theory

Initially, all ovarian cancers were thought to originate from the epithelium of the ovarian cell surface. During ovulation, these surface epithelial cells experience physical trauma, which is repaired immediately. During a woman's life cycle, ovulation occurs repeatedly, which causes repetitive trauma to the epithelium, ultimately causing cellular DNA damage. Epithelial cells that have undergone DNA damage are very susceptible to change, which facilitates invagination to the cortical stroma. This invagination eventually becomes trapped and forms a sphere of epithelial cells in the stroma called cortical inclusion cysts. While inside the ovary, the epithelial cells are exposed to ovarian hormones that stimulate cell proliferation, which in turn transforms into cancer cells.[3]

Fallopian Tube Theory

Previously, most researchers believed that ovarian cancer originated from the ovary itself. Thus, only a few tried to look for ovarian cancer precursor lesions elsewhere . It was reported that epithelial dysplasia was found at a high incidence in the Fallopian tubes (50%) of women with BRCA1/2 gene mutations undergoing prophylactic salpingo-oophorectomy. This epithelial dysplasia resembled high-grade serous ovarian carcinoma, which they called tubal intraepithelial carcinoma (TIC). Other studies also found similar histology characteristics of ovarian cancer and high-grade serous peritoneal cancer, regardless of BRCA status. Studies that examined the contralateral ovary of patients with ovarian cancer showed either normal histology or morphologic changes that did not resemble high-grade serous neoplasm characteristics. Based on these studies, it can be concluded that the fallopian tube would likely be the location of the ovarian cancer precursor lesions, which eventually spread to the adjacent ovary.

Two-Pathways Theory

This theory was originally proposed by Kurman and Shih in 2004, who sought to integrate the histological, clinical and genetic findings of ovarian cancer. They divided ovarian cancer into 2 types, namely type I and type II. Type I ovarian cancer consists of low-grade serous, mucinous, endometrioid, clear cell, and transitional histology types. Meanwhile, type II ovarian cancer consists of high-grade serous, undifferentiated and carcinosarcoma histology types.[4]

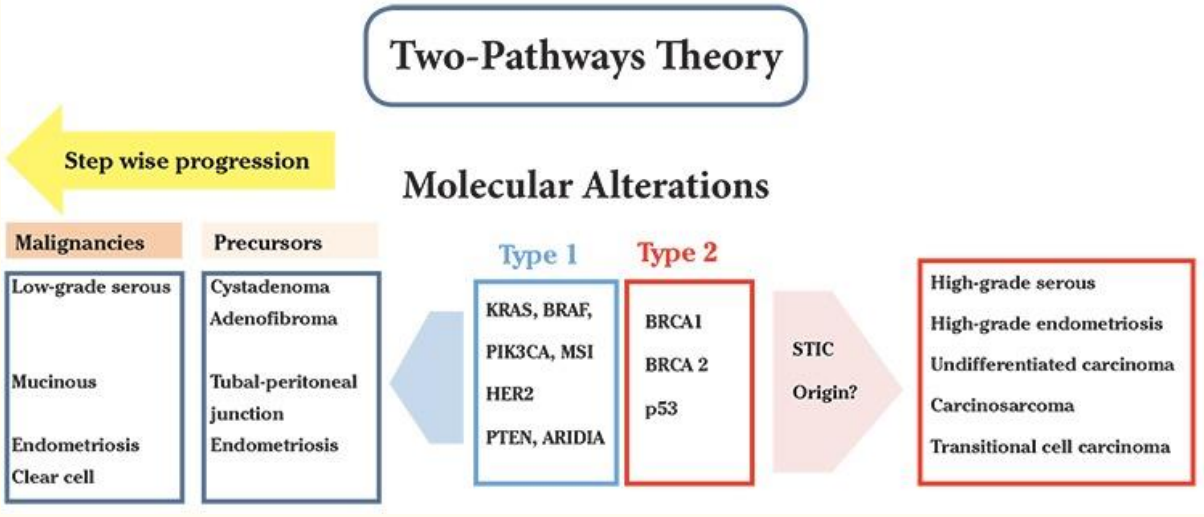


Fig:1 two path ways theory

Symptoms:

Ovarian cancer may cause no symptoms in the early stages. If any occur, they tend to be very general.Symptoms of ovarian cancer can appear at any stage Trusted Source, they tend to develop in the later stages, as growths put pressure on the bladder, uterus, and rectum.

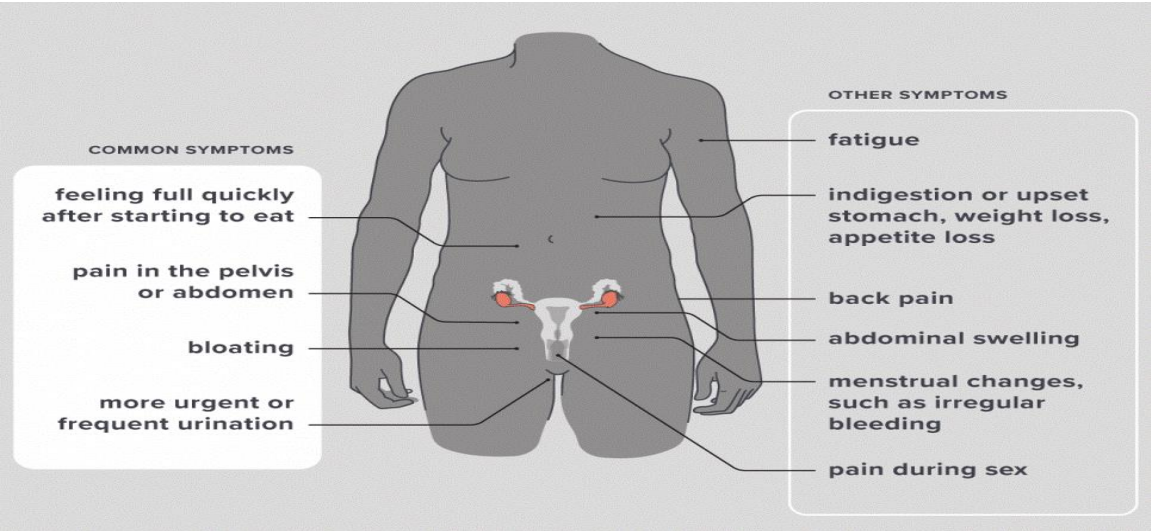
The most common symptoms are:

- bloating
- pain in the pelvis or abdomen
- feeling full soon after starting to eat
- having more urgent or frequent urination

Other symptoms include:

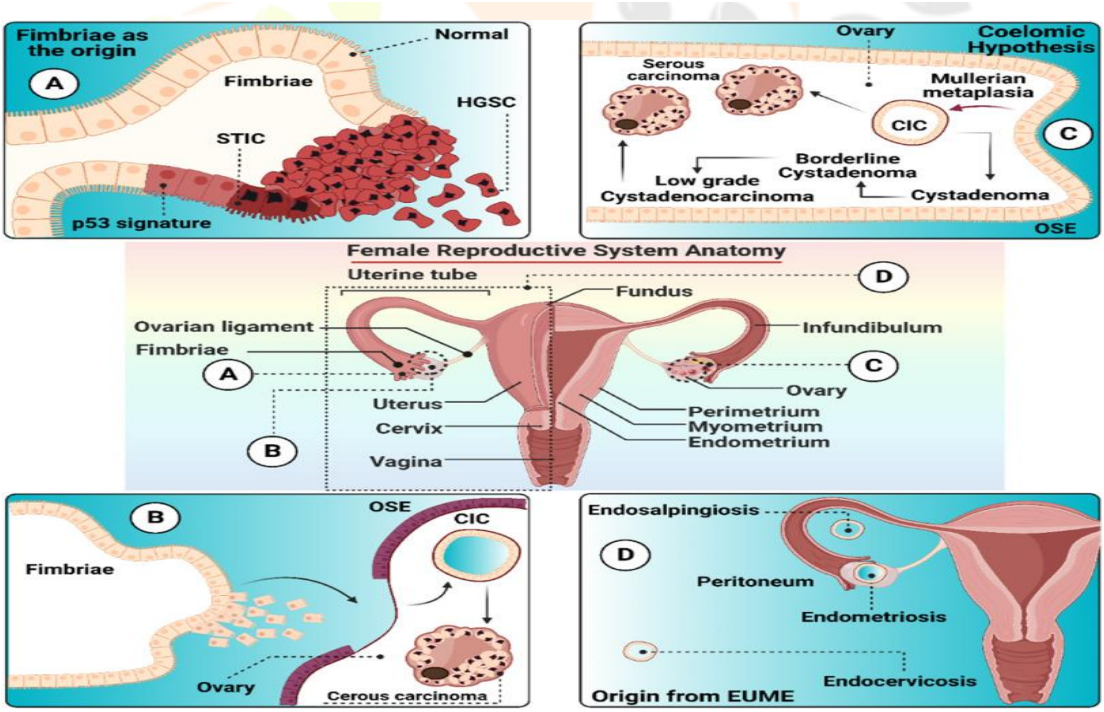
- indigestion, or an upset stomach
- fatigue
- back pain
- constipation
- abdominal swelling
- pain during sex
- menstrual changes, such as irregular bleeding

These symptoms can have a wide range of causes and do not necessarily stem from ovarian cancer. However, if any of these symptoms are new, frequent, or persistent, seek medical advice.[5]



The types of ovarian cancer

Different subtypes of ovarian cancer were discussed in nine studies. Studies show that up to 90% of all OC have epithelial origin and the remaining OC have non-epithelial origin. Among epithelial OC, 3% are mucinous and others are non-mucinous. Non-mucinous are further found to have serous (70% of non-mucinous), endomterioid (10%), clear cell (10%), and unspecified subtypes (5%).According to recent studies, serous carcinomas are divided into two separate subtypes: high grade and low grade. Compared to epithelial cancers, non-epithelial cancers are less invasive.



cancer type	**percentage of all ovarian cancers**	**characterstics**
Epithelial cell	85 to 95	Most common in patients older than 50 years; 15 percent of epithelial cell ovarian cancers are borderline or have low malignant potential, with a 10-year survival rate up to 99 percent for stage I
Serous		40 percent of all ovarian cancers; most common ovarian cancer
Endometrioid		20 percent of all ovarian cancers; 15 percent of endometrioid carcinomas coexist with endometriosis; 40 percent bilateral
Mucinous		25 percent of all ovarian cancers; origin unclear; may occur in association with endometriosis; associated with pseudomyxoma peritonei
Stromal cell	5 to 8	Derived from the sex cord of embryonic gonads
Granulosa-theca		Wide age range; may produce precocious sexual development in prepubertal girls; may be associated with endometrial hyperplasia, cystic disease of the breast, and endometrial carcinoma in adults; ascites in 40 percent of fibromathecoma tumors; may be associated with ascites and hydrothorax (Meigs syndrome)
Sertoli-Leydig (androblastomas)		Common in adolescence; may be masculinizing; may block normal female sexual development
Germ cell	3 to 5	Found mostly in children and young adults 20 to 30 years

		of age highly malignant; usually unilatera
Endodermal sinus tumor		Most common germ cell ovarian cancer in children; usually larger than 15 cm; median age of patients is 18 years, one third of patients are premenarchal
Embryonal (multipotential)		Extraembryonic: yolk sac carcinoma Primitive: embryonal carcinoma (highly malignant), precocious puberty Somatic: immature teratoma Trophoblast: choriocarcinomas Undifferentiated: dysgerminomas (most common malignant germ cell ovarian cancer), 10 to 20 percent bilateral, radiosensitive
Mature		Mostly benign, dermoid cysts
Metastasis to ovaries (Krukenberg tumor)	5 percent	Typically from breast or gastrointestinal primary sites

Risk factors

Demographic factor Age

The epithelial ovarian cancer is an age-related disease, and is considered mainly a postmenopausal disease. Increased incidence of this cancer is more pronounced in women over 65 years of age. According to previous studies, median age at diagnosis is 50–79 years. The relationship between age and the outcome of ovarian cancer is uncertain. Older women are treated less aggressively in contrast with younger ovarian cancer patients, and, thus, survival is lower in these group. An age of over 64 years is one of the predictors of mortality in people with ovarian cancer.

Reproductive factorsMenstrual-related factors Tung et al stated that non-mucinous tumors are strongly associated with menstrual periods (odds ratio=1.5 for the highest vs the lowest quartile) and ovulation cycles (odds ratio=2.8 for the highest vs the lowest quartile). In numerous studies, researchers indicated an inverse relationship between ovulation cycles and the risk of ovarian cancer. The result of a case-control study showed that, in women who have not had an ovulation cycle for 8.7 years, the risk of ovarian cancer was reduced by 4-times.[6]

Gynecologic factors

Pelvic inflammatory disease *:*

The role of inflammation and pelvic inflammatory disease in the occurrence of ovarian cancer is controversial among experts. Ness et al, in a case-control study, supported the hypothesis that suggests inflammation contributes to the onset of ovarian cancer.

Endometriosis

The relationship between endometriosis and ovarian cancer has been shown in various studies through various mechanisms. The results of a cohort study showed that, in people with endometrium, aging, living in urban areas, low or high income, depression, pelvic infection, and lack of childbearing increase the risk of ovarian cancer.[7]

Ovarian cysts

Some types of benign ovarian cysts may act as a precursor of malignant ovarian tumors. According to a case-control study, ovarian cyst is associated with increased risk of borderline ovarian tumors (OR=1.3 [0.9–1.8]), and this risk increased among women who were undergoing surgery.

Hormonal factors

Contraceptive methods

Results of most studies indicate that the use of oral contraceptive methods is associated with a reduced risk of all histological types of ovarian cancer. Results of a case-control study in Canada indicated that the use of hormonal contraceptive pills is associated with a significant reduction in all histological types of epithelial ovarian cancer, except for mucinous tumors. According to the findings of this study, OR for each year of use of these pills was 0.89 [0.85–0.93] for non-mucinous tumors and 0.98 [0.93–1.04] for mucinous tumors. The result of a case-control study showed that oral contraceptive pill (OCP) decreases the risk of fatal and advanced ovarian cancer compared to less advanced cases.[8]

Hormone replacement therapy (HRT)

The result of a case-control study showed that combined estrogen-progesterone therapy after menopause does not increase the risk of ovarian cancer. Hempling et al examined the effect of exposure to post-menopausal hormone therapy, and stated that HRT is not associated with ovarian cancer, even in long term use.

Infertility treatments

Ovarian cancer is a rare and, at the same time, a fatal disease. Regardless of infertility treatments, nulliparity itself and infertility are risk factors of ovarian cancer, so it is difficult to investigate the relationship between infertility treatment and ovarian cancer. The "incessant ovulation theory" states that ovulation without interruption can contribute to the development of ovarian cancer by damaging the ovary epithelium, and, therefore, any factor that contributes to the reduction of ovulation can have a protective effect against ovarian cancer. Several studies have indicated an association between the increased risk of ovarian cancer and the use of clomiphene citrate and gonadotropin.[9]

Family history : The most important risk factor for ovarian cancer is a family history of breast or ovarian cancer. Personal history of breast cancer is associated with an increase in the risk of ovarian cancer (OR=3.7 [1.8–7.7]). The results of a case-control study showed that the risk of ovarian cancer increases in women with a family history of breast, uterine, or ovarian cancer in their mother or sister (P<0.001).

Lynch syndrome:

Lynch syndrome is an autosomal dominant cancer predisposition syndrome that is responsible for 1–3% of all colorectal cancer. Lynch syndrome is responsible for 10–15% of the total inherited ovarian cancer cases, and the lifetime risk of this cancer in individuals with a family history of Lynch syndrome is 6–8%. Most of the ovarian cancers associated with Lynch syndrome are non-mucinous, and 82–84% of them are in stage I or II. Lynch occurs due to a

hereditary mutation in one of the four mismatch repair genes (*MHL1*, *MSH2*, *MSH6*, and *PMS2*), and *MSH2* and *MLH1* are the most common mutations in these individuals. The most common types of ovarian cancer in these individuals are endometrioid and clear cell ovarian cancers.[10]

Lifestyle factors

Nutrition and diet

According to the findings of a case-control study, there is a positive correlation between daily intake of fish and the risk of ovarian cancer ($P<0.05$), and this correlation is negative for daily intake of milk ($P=0.05$). Results of a case-control study showed that the risk of ovarian cancer is associated with a higher cholesterol intake (OR=1.42 [1.03–1.97]), and this risk is reduced by consumption of vegetables (OR=0.77 [0.60–1.04]), vitamin supplement (OR=0.49 [0.30–0.81]), beta-carotene (OR=0.31 [0.11–0.91]), and B-complex vitamins (OR=0.61 [0.36–1.05]). McCann et al refer to the protective role of phytoestrogens in the development of ovarian cancer, and believe that a plant-based diet plays an important role in the reduction of hormone-related cancers. The results of a case-control study showed that saturated fat is associated with an increased risk of ovarian mucinous tumors. Ong et al revealed that an increased concentration of vitamin D in plasma may reduce the risk of ovarian cancer. This risk reduction is also seen in the case of calcium and lactose consumption.[11]

Obesity and physical activity

The results of a study showed that obesity reduces the risk of survival in ovarian cancer (HR=3.40 [1.16–9.99]), and increases the risk of death caused by the disease (HR=0.58 [0.35–0.96]). Central adiposity is associated with an increased risk of ovarian cancer, indicating the conversion of androgen in the peripheral tissues. 36% increase in the risk of ovarian cancer among obese people who have never used postmenopausal estrogen treatment, and stated that obesity and tallness increase the mortality of ovarian cancer.

Alcohol, caffeine, and cigarettes

Several researchers around the world believe that alcohol does not increase the risk of ovarian cancer, but Goodman and Tung argue that alcohol's relation to ovarian cancer is related to the type of alcohol. Schouten et al believed that drinking alcohol in the form of wine, beer, or liquor is not associated with an increased risk of ovarian cancer. However, the result of a case-control study showed that caffeine and coffee consumption may increase the risk of ovarian cancer in women before menopause.[12]

Treatment

- **Surgery** to remove as much of the cancer as possible
- Chemotherapy
- Targeted therapy**,** which uses drugs or other substances that attack specific cancer cells with less harm to normal cells
- Conventional therapy for ovarian cancer is surgical tumor cytoreduction followed by a combination of platinum and nonplatinum (taxane-based) chemotherapy, such as carboplatin (formerly Paraplatin) and paclitaxel (Taxol), respectively. There is no reliable evidence that chemotherapy before debulking surgery is superior to conventional treatment in women with advanced epithelial ovarian cancer. Surgical staging involves total abdominal hysterectomy, bilateral salpingo-oophorectomy (BSO), and the removal of pelvic and para-aortic lymph nodes and omentum; as well as other supplemental procedures, such as appendectomy, when indicated.19 Appendectomy is a typical supplemental procedure for mucinous ovarian cancer because of the possibility of metastasis.

Ovarian cancer with low malignant potential typically occurs in women 30 to 50 years of age. It presents at stage I in 82 percent of patients and has a survival rate of up to 99 percent.20 This favorable prognosis allows for consideration of conservative fertility-sparing measures, such as unilateral salpingooophorectomy. Surgical cytoreduction is considered therapeutic, and adjuvant chemotherapy is reserved for patients with postoperative residual disease or identifiable invasive implants. Because of the possibility of late recurrence, surgical treatment completion with total abdominal hysterectomy and unilateral salpingo-oophorectomy should be considered after the reproductive years. Radiation is most often used for palliative purposes or for localized persistent disease after chemotherapy.(13)

Prevention and Screening

The CA 125 test is a poor screening test because it does not rule out ovarian cancer, and a false-positive test may lead to unnecessary invasive interventions. The U.S. Preventive Services Task Force (USPSTF) recommends against routine screening for ovarian cancer.11 The USPSTF also recommends against routine referral for genetic counseling or routine BRCA testing in women whose family history is not consistent with increased risk of BRCA1 or BRCA2 mutations.14 The USPSTF recommends referral for genetic counseling and evaluation for BRCA testing in women whose family history is associated with an increased risk of BRCA1 or BRCA2 mutations.14 Annual transvaginal ultrasonography and CA 125 measurement may detect ovarian cancer at an earlier stage in women at high risk of ovarian cancer, but are ineffective at detecting ovarian cancer early enough to improve clinical outcomes.38 A randomized controlled trial of more than 200,000 postmenopausal women in the United Kingdom evaluated the use of CA 125 (interpreted using an ovarian cancer risk algorithm) as an annual screening test, with transvaginal ultrasonography as a secondline test.(14)

Conclusion

Ovarian cancer is the most frequent gynecological malignancy that has a fatal outcome. Most studies focus on the predominant type, HGSOC, but unfortunately, the most common cell lines used to study it to date have proved insufficiently representative. Due to the great heterogeneity of the disease, in vitro studies require well-defined models to make the findings comparable and transferable to the clinical environment. The main reason for the poor prognosis of ovarian cancer and its unsuccessful treatment is primarily the emergence of chemoresistance to carboplatin. Although there is a good response to primary treatment, the disease recurs in 80%, at which point, it is largely resistant to carboplatin.

Reference

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics, *J Clin*. 2018;68:394–424
2. Torre LA, Trabert B, DeSantis CE, Ovarian cancer statistics, J Clin. 2018;68:284–296
3. Momenimovahed Z, Tiznobaik A, Taheri S, Salehiniya H. Ovarian cancer in the world: epidemiology and risk factors. J Womens Health. 2019;11:287-299
4. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. J Clin. 2020:5:7-30.
5. DeSantis CE, Pathology of cancers of the female genital tract. J Gynaecol Obstet. 2012;119:137–150.
6. Erickson BK, Conner MG, Landen CN Jr. The role of fallopian tube in the origin of ovarian cancer. J Obstet Gynecol. 2013;209:409–414.
7. Yvette Brazier, Torre LA, Jemal A, symtoms of ovarian cancer, 2023:4:46-49.
8. Reid BM, Permuth JB, Sellers TA. Epidemiology of ovarian cancer: a review. Cancer Biol Med. *2017;48;103-109.*

9. Mohammadian M, Ghafari M, Khosravi B, Variations in the incidence and mortality of ovarian cancer and their relationship with the human development index in European Countries, J Biomed Res Ther. 2017;4:1541–1557.
10. Kim SJ, Rosen B, Fan I, Epidemiologic factors that predict long-term survival following a diagnosis of epithelial ovarian cancer. Br J Cancer. 2017;116:964.
11. Reigstad MM, Storeng R, Myklebust TÅ, Cancer risk in women treated with fertility drugs according to parity status—A registry-based cohort study. J Cancer Epidemiol Biomarkers Prev. 2017;26:953–962.
12. . Jia D, Nagaoka Y, Katsumata M, Orsulic S. Inflammation is a key contributor to ovarian cancer cell seeding. *Sci Rep*. 2018;8:12394.
13. . Torre LA, Trabert B, DeSantis CE, Ovarian cancer statistics, 2018. CA Cancer J Clin. 2018;68:284–296.
14. Zheng G, Yu H, Kanerva A, Försti A, Sundquist K, Hemminki K. Familial risks of ovarian cancer by age at diagnosis, proband type and histology.J medicinal chemistry. 2018;13;23-29.