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Original Article

Screening and Early Diagnosis of Ovarian Cancer: An Updated Review

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ABSTRACT

Ovarian cancer has emerged as one of the most common malignancies affecting women in India and the most lethal gynecological malignancy, is a significant global health challenge, with >324,000 new cases and >200,000 deaths being reported annually. OC is characterized by late-stage diagnosis, a poor prognosis, and 5-year survival rates ranging from 93% (early stage) to 20% (advanced stage). Despite advances in genomics and proteomics, effective early-stage diagnostic tools and population-wide screening strategies remain elusive, contributing to high mortality rates. Novel screening methods including organoids and multiplex panels are being explored to overcome current diagnostic limitations. It is not curable but three most extensively evaluated screening methods for ovarian cancer are pelvic examination, serum CA 125, and transvaginal sonography (TVS). The lack of sensitivity of pelvic examination and serum CA 125 has limited their use in ovarian cancer screening. Currently, the most effective screening method for ovarian cancer is TVS. Genetic testing for gene mutations that affect treatment is the standard of care for all women with epithelial ovarian cancer. Nearly all women will have a recurrence, and the treatment of recurrent ovarian cancer continues to be nuanced and requires extensive review of up-to-date modalities that balance efficacy with the patient's quality of life. This review highlights the critical need for continued research and innovation to enhance early diagnosis, reduce mortality, and improve patient outcomes in ovarian cancer.

Keywords: Ovarian cancer, Early diagnosis, Screening methods, CA-125, Transvaginal sonography

INTRODUCTION

It begins when the unhealthy cells in the ovaries begin to multiply uncontrollably. Ovarian cancer accounts for 3-4% of cancers in women. And is the 4th most frequent cause of cancer-related death in females. Approx. 3,24,603 women diagnosed with ovarian cancer. Globally it's the 8th most common cancer in women around 1 in 78 women may develop ovarian cancer during their life [1]. The risk of this cancer is higher in industrialized countries because the diet tends to be high in fat. Risk is increased for women who were unable to become pregnant, who had their first child late in life, As a consequence, the identification of women at risk for the disease is based mainly on clinical grounds, with family history being the most important risk factor. In this review, we will discuss the various hypotheses regarding ovarian etiology and pathogenesis. Along with this, we will discuss the epidemiology of ovarian cancer, including hereditary, reproductive, hormonal, inflammatory, dietary, surgical, and geographic factors that influence ovarian cancer risk [2]. Women with a family history of ovarian cancer or a known associated genetic syndrome should be offered genetic counseling or a discussion of available preventive interventions, respectively, Hereditary nonpolyposis colorectal cancer syndrome (i.e. Lynch II syndrome) is an autosomal dominant mutation that predisposes to nonpolyposis colorectal, endometrial, breast, and ovarian malignancies [3]. The risk of developing ovarian cancer in individuals with hereditary nonpolyposis colorectal cancer syndrome is 12 percent [2] The risk of colorectal (15 percent) breast (7 percent), gastric (6 percent).

Epidemiology

Incidence and mortality

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With 225,500 new cases diagnosed and 140,200 deaths from cancer worldwide in a year, it is one of the most fatal cancers. Moreover, incidence and mortality from ovarian cancer differ in various countries, and Russia and the United Kingdom top the list of ovarian cancer, whereas China is at the lowest-end of incidence and survival rates. In the United States, there are 22,280 new cases, and the expected deaths in 2016 are 14,240 [4-6]. Notably, the incidence rate of ovarian cancer decreased by 1.09% in women aged 65 years and 0.95% in women aged ≥ 65 years from 1998 to 2008, which may be related to the shift in prescriptions of hormonal therapies, where decreased incidence of ovarian cancer occurred simultaneously after the declaration of the casual association of ovarian cancer and hormone replacement therapy, thus less prescriptions were written [8]. There is only a slight progress in death rates from the past decade. The Surveillance, Epidemiology, and End Results Program of the US Surveillance, Epidemiology, and End Results Program where the database reports that overall survival for all patients with ovarian cancer is 45.6%, but this varies dramatically depending on the stage at initial diagnosis; 5-year overall survival in patients with stage I cancer is 92.1% while in patients with stage III and stage IV cancer, it is only 25% for patients with stage III and stage IV cancer [9,10]. The symptoms of overian cancer was mentioned in (fig. 1) [10].

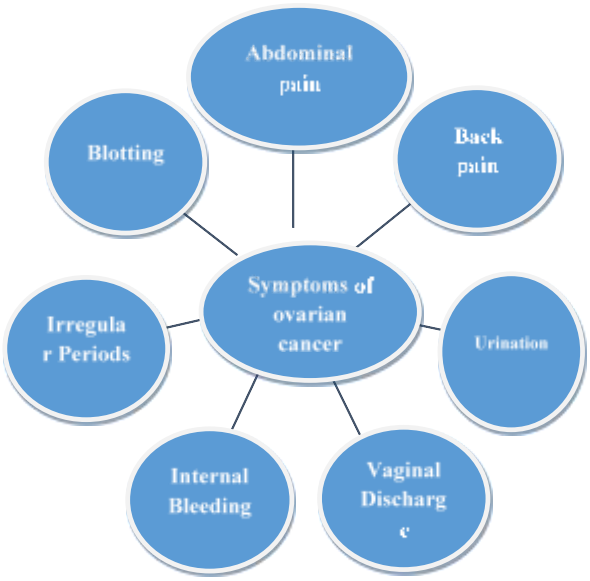


Figure 1: Symptoms of ovarian cancer

Ovulation and Ovarian Cancer Etiology

"The relative prevalence of ovarian cancers among nulliparous women was the impetus for the development of the hypothesis that recurrent ovulatory activity is involved in the malignant tran-sformation of the ovarian surface epithelium [11]. On the other hand, it has also been proposed that perhaps it is the underlying hormonal imbalance that can cause infertility in some women. It is this condition that has been considered responsible for the risk of ovarian cancer in nulliparous women [12]. The fact that the use of oral contraceptives lowers the risk of ovarian cancer supports the former, more widely publicized theory [13-16]. It is also worth noting that ovarian cancers that arise from surface epithelial cells are a relatively rare occurrence in the animal kingdom. Related to this, in nature, animals ovulate seasonally, with the majority becoming pregnant shortly after ovulatory function is initiated in the spring of each year. In other words, the number of ovulations that occur in a lifetime is relatively low except in the case of the insatiable ovulator, the common hen, which also has epithelial ovarian cancer in high numbers [17,18]. It is tempting to speculate how ovulatory activity could contribute to ovarian cancer etiology. If surface epithelial inclusion cysts are important in disease etiology, it is obvious that there would be a greater opportunity for such cysts to form in the more frequently ovulating person. In addition, the surface epithelial cell mitotic activity required to repair the wound created by the follicular rupture accompanying

ovulation may be a factor in disease initiation. As noted above, mutations are more likely to occur in dividing as opposed to quiescent cells. Furthermore, because growth increases the pool of cells carrying a potential first mutation (first hit), the probability of an additional mutation occurring in a cell with a preexisting mutation is increased. It is interesting to speculate whether there might be a set of mechanisms for vigorously ensuring the fidelity of DNA replication, repair, or chromosomal segregation that are not active in surface epithelial cells because these cells would have been under little selective pressure with regards to evolution nature, the cells have a greatly restricted need for DNA duplication, contrasted with the selective Pressure exerted upon the skin or intestinal epithelial surface which would be expected to have been strictly selected for the ability for wound healing, or lumenal replacement, respectively [19, 20]. It is a notable point, under these circumstances, that proteins have been identified with a function in DNA duplication fidelity, or the segregation of chromosomes, with the aim of diminishing the possibility of recombination or malignant transformation [21,22]. There was, over the years, a fairly persuasive argument made regarding the importance of incessant ovulation in the causation of ovarian cancers. Besides the rewriting of the original hypothesis, apart from rather weak epidemiologic evidence, there was a complete lack of bio-logic evidence. It is only recently that a mechanism was outlined in which ovarian surface epithelial cells, as derived from the rat, underwent malignant transformation as a result of their exposure to a prolonged environment [23-24].

Pathophysiology of Ovarian Cancer

By progressive genetic changes in epithelial cells of the ovary, due to multifactor etiology, genetic predispositions, frequent ovulation, hormone disturbances, chronic inflammation, and environmental exposures, genetic alterations take place [25]. The alterations are associated with two pathways. In the first, genetic changes are observed in oncogenes and signalling pathway genes, including KRAS, BRAF, PTEN, β-catenin, and TGF-β receptor II, causing problems in the signalling pathways inside cells. This leads to uncontrolled but poorly growing tumours, which are further associated with mucinous, endometrioid, and low-grade serous carcinomas [26]. This pathway leads to mucin and endometrioid ovarian cancers. The second pathway, which has high aggression, involves genetic changes in tumour suppressor genes, including TP53, BRCA1, BRCA2, and DNA mismatch repair genes, such as MLH1 and MSH2.Such mutations affect the ability of the cell to detect or repair DNA damage [27]. This makes the cell resistant to apoptosis. As a result of mutations, the cell proliferates. Such mutations lead to the development of serous carcinoma of the ovary. Eventually, these mutations cause growth of the tumour as well as invasion [28]. Additionally, they can lead to spread of the tumour. This justifies the aggressive nature of the malignant condition of the ovary [29].

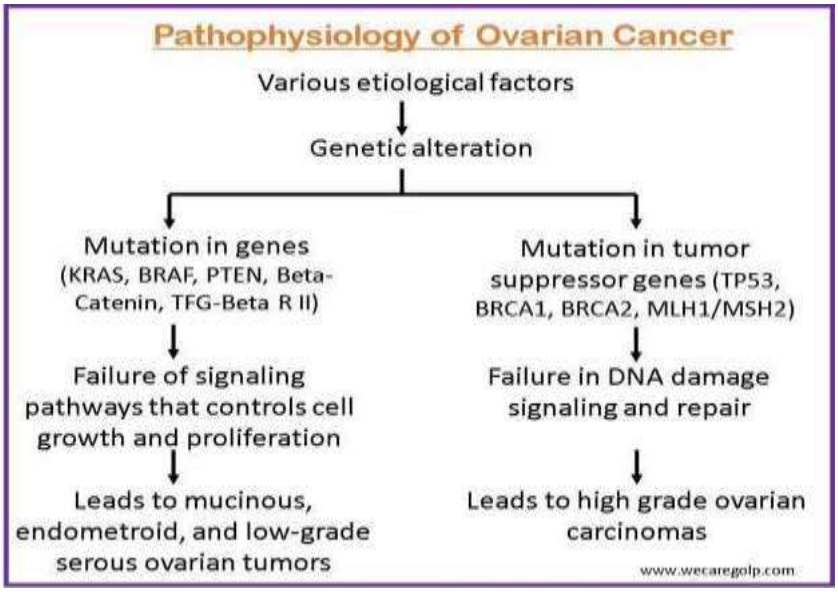


Figure 2: Pathophysiology of ovarian cancer [25-29]

Diagnosis of Ovarian Cancer

In patients with suggestive symptoms, diagnostic work-up includes physical examination of the patient. This includes pelvic and rectovaginal exams [30-31]. Tissue biopsy is also required to confirm the diagnosis of ovarian cancer.

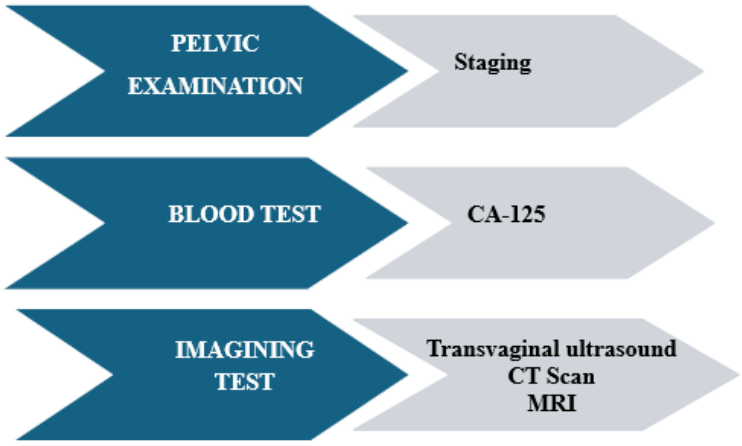


Figure 3: Various techniques to detect ovarian cancer

Stages of Development of Ovarian Cancer

Pathological evaluation and tumour staging of ovarian cancer is based on surgical assessment of the cancer at initial diagnosis, including removal of lymph nodes, tissue biopsy and abdominal fluid, and uses the International Federation of Gynecology and Obstetrics staging system. The staging system has recently changed with acceptance of the common, Müllerian-derived, multicentric origin of ovarian, fallopian tube and peritoneal cancers and that these cancers should be grouped using one system [32]. The new FIGO staging has three other prominent features: the IC stages have been differentiated according to the underlying cause of ovarian capsule rupture and the presence of malignant ascites (ascites containing tumour cells), the IIC stage has been removed, and the III stage has more clearly defined criteria that include the size of the metastases as well as the involvement of the lymph nodes. In addition, the III stage has again been differentiated according to whether or not the patients have metastases to the lymph nodes and whether or not the patients have peritoneal carcinomatosis [33,34]. Further, Stage IV has been subdivided into Stage IVA and Stage IVB. The current FIGO system of staging ovarian tumours proposes that the primary tumour site (ovary, fallopian tube, or peritoneum), and histologic grade should be reported in the surgical report and/or the post-surgical pathology report [35]. The surgical staging of ovarian cancer performed by gynecologic oncologists has been demonstrated to be more accurate than surgical staging performed by general surgeons who are not gynecologic oncologists, and outcomes in these patients have also been better [36]. In fact, the question of correct surgical staging is far from trivial, and a recent study demonstrated that in one series, only 54% of women with ovarian cancer were correctly staged according to a gynecologic oncologist's assessment [37]..When the patients underwent the operation by non-gynaecologic oncologists, general surgeons, or general gynaecologists, the diaphragm was not evaluated in 86% of the cases, and omentum biopsy was not performed in 68% of the cases[38], implying that the cancer was missed in the diaphragm, pelvis, peritoneal surfaces, peritoneal fluid and omentum (Figure 4).

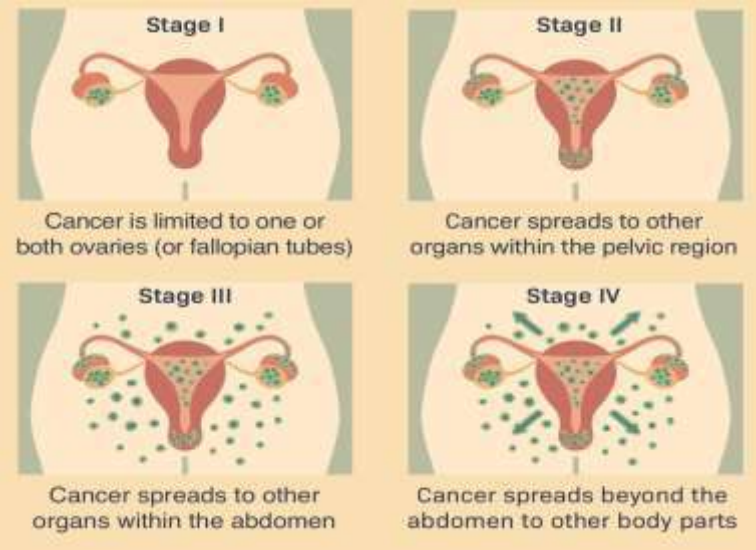


Figure 4: Stages of development of Ovarian Cancer (stage 1-4)

Screening methods of Ovarian Cancer

Despite the progress made in the assessment and management of ovarian cancers, it has been seen that the majority of women continue to be diagnosed with advanced ovarian cancers, and thus the survival is very poor. It has been observed that over the last 2 decades, there has not been any improvement in the overall patient survival in the case of ov- arian cancers.[39] The death rate of women suffering from ovarian cancers has dropped from 8.8 in 100,000 in 1958-1960 to 7.9 in 1988- 1990, according to the data provided by SEER.[40]' Owing to the remarkably high chances of survival for women with early-stage ovarian cancer, there has been a growing interest in the development of screening tests capable of identifying ovarian cancer at a stage that is amenable to treatment. The ideal screening test should be non-toxic, time-effective, and widely acceptable to the screened subjects. More importantly, it should be highly sensitive, specific, and possess a high positive and negative predictive value [41- 44]. Statistical definitions employed in ovarian screening studies are explained. Patients who have a negative screening test result do not go on to have exploratory surgery to verify the lack of disease, so the modified definition of a true negative is that there is no ovarian cancer 1 year following a negative test result. A false negative is having histologically proven ovarian cancer within 1 year post negative test result.

- **CA 125**

CA 125 is an antigenic determinant on a high molecular weight glycoprotein recognized by a monoclonal anti- body, OC 125. [46] CA 125 is expressed by epithelial ovar- ian cancers and is present in highest concentrations on the tumor cell s~rface [47]. Serum levels of this marker are elevated (>35 p/ml) in approximately 80% of patients with epithelial ovarian cancer [48]. However, serum CA 125 is increased in only 25-50% of patients with clini- cally detectable Stage I ovarian cancer [49] In addition, serum CA 125 is elevated in patients with a number of benign ovarian tumors, such as endometriomas, in- flammatory ovarian masses, or serous cystadenomas [50]. Most of the benign inflammatory conditions that pro- duce elevated serum CA 125 levels occur in premeno- pausal women.

Test is used for:

- **Monitoring treatment:** To see if chemotherapy or other treatments for ovarian cancer are working.
- **Checking recurrence:** Rising levels can signal that ovarian cancer has returned after treatment.
- **Evaluating masses:** To help determine if a pelvic lump or growth might be ovarian cancer. [51]
- **High-risk screening:** For individuals with a very high risk (e.g., strong family history) of ovarian cancer, often with a transvaginal ultrasound.

Important considerations

Not a standalone diagnostic tool: Many benign conditions (endometriosis, fibroids, PID) and even menstruation can raise CA-125 levels. Limited for early detection: Because normal tissues produce it, it lacks the sensitivity and specificity for diagnosing early-stage ovarian cancer in the general population. Normal range: Generally, levels below 35 U/mL are considered normal, but a high result needs further investigation with other tests and imaging [52].

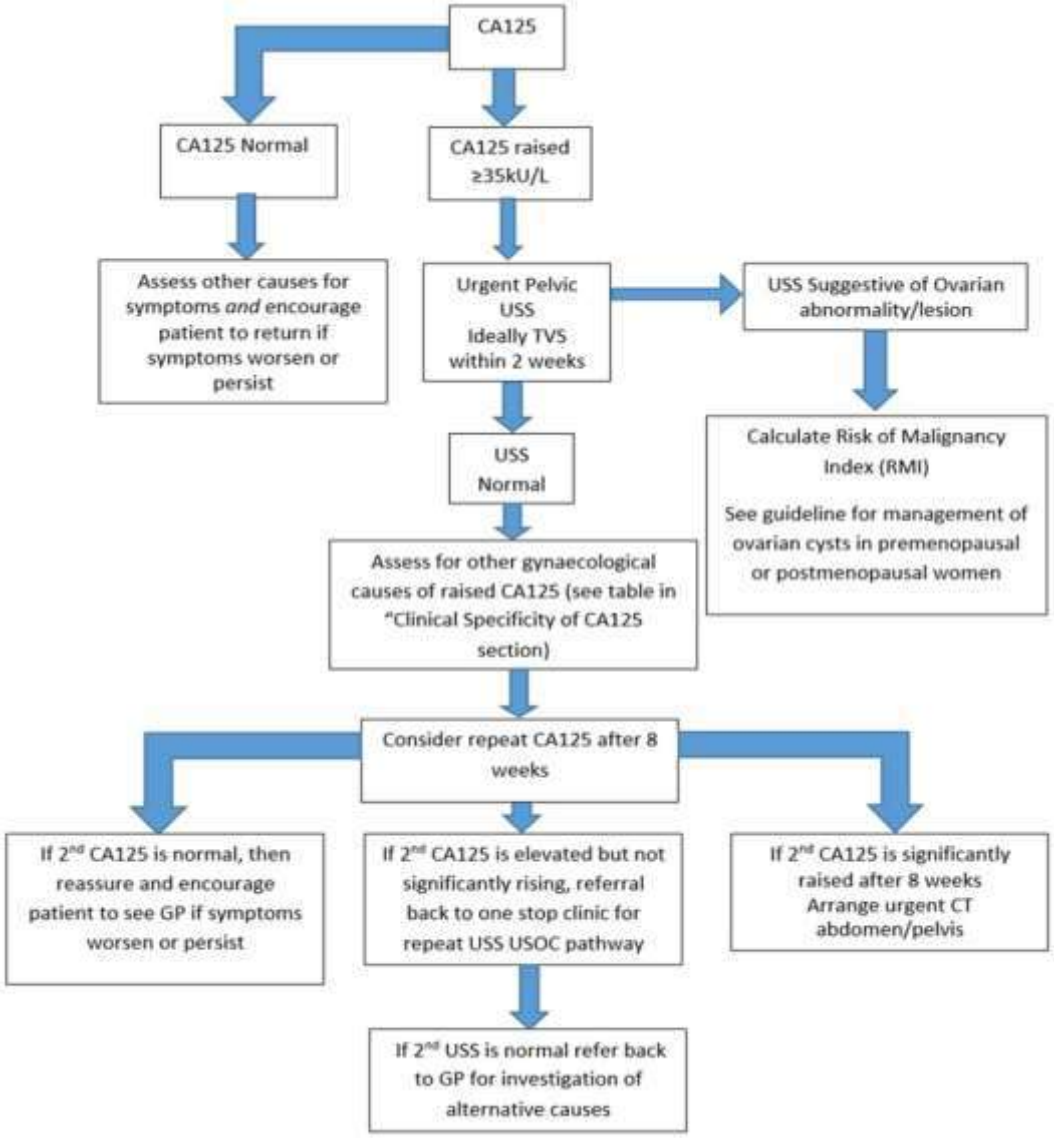


Figure 5: Elevated CA-125: guidance on how to investigate women where raised CA-125 is found [53 - 56]

- **Transvaginal Sonography**

Transvaginal sonography is the most effective screening method for ovarian cancer. It usually is performed with use of a standard ultrasound unit with a 5.0-MHz vaginal transducer. Abdominal sonography was first used by Campbell and cowrkers as a screening method for ovarian cancer. This technology was significantly more accurate than pelvic examination in the detection of ovarian tumors [57]. However, abdominal sonography requires a full bladder for optimal visualization of pelvic structures and is not ideally suited for screening. Transvaginal sonography is painless, time efficient, and best performed on an empty bladder. A complete screening examination takes 5-10 minutes, and a permanent hard copy of each sonogram is generated for inclusion in the patient record. A woman with abnormal screening results is scheduled to have a repeat sonogram in 4-6 weeks.

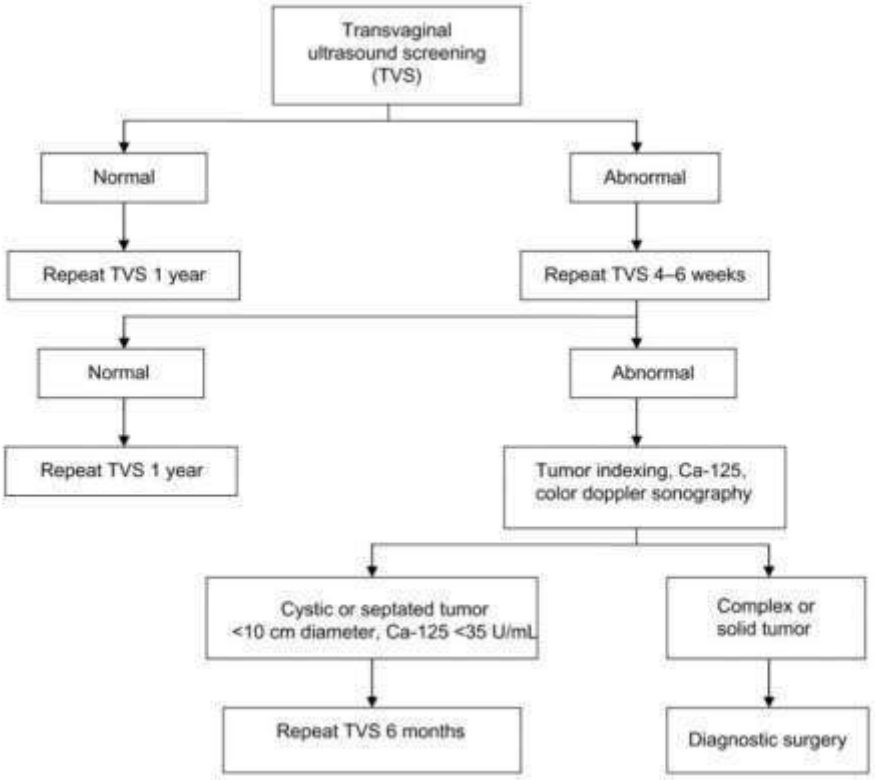


Figure 6: Transvaginal ultrasound Screening [58,59]

- **Ultrasonograph**

Ultrasonography, particularly transvaginal sonography (TVS), plays a crucial role in the evaluation and screening of ovarian cancer due to its wide availability, noninvasive nature, and ability to provide detailed imaging of ovarian morphology. TVS is effective in detecting adnexal masses and distinguishing benign from malignant features based on characteristics such as size, solid components, septations, papillary projections, and vascularity when combined with Doppler imaging. Although ultrasonography has limited specificity for population-wide screening and cannot reliably detect early-stage disease on its own, it remains the most effective imaging modality for initial assessment, risk stratification, and follow-up of suspected ovarian lesions, especially when used alongside clinical findings and tumour markers like CA-125.

Table 1: Sonographic image of benign and malignant ovarian morphology. Numeric (representation of increasing morphologic complexity is noted in first column [60]

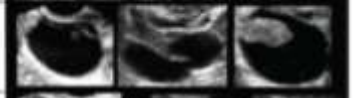
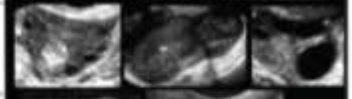
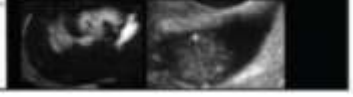
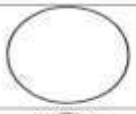
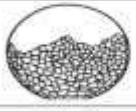
0	Benign simple cyst		
1	Benign hemorrhagic cyst		
2	Benign cyst with septation(s)		
3	Malignancy with papillary projections		
4	Malignancy with solid components		
5	Solid malignancy with ascites		

Table 2: The university of Kentucky ovarian tumour morphology index [61]

	Tumor volume	Tumor structure
0	<10 cm³	
1	10–50 cm³	
2	>50–100 cm³	
3	>100–200 cm³	
4	>200–500 cm³	
5	>500 cm³	

Risk Factors of Ovarian Cancer

Ovarian cancer risk factors include age, genetics (BRCA1/2, Lynch syndrome), family history, reproductive factors (never pregnant, early menstruation, late menopause, infertility), endometriosis, obesity, and lifestyle choices like smoking and postmenopausal hormone therapy, with protective factors like birth control pills and pregnancies reducing risk [62].

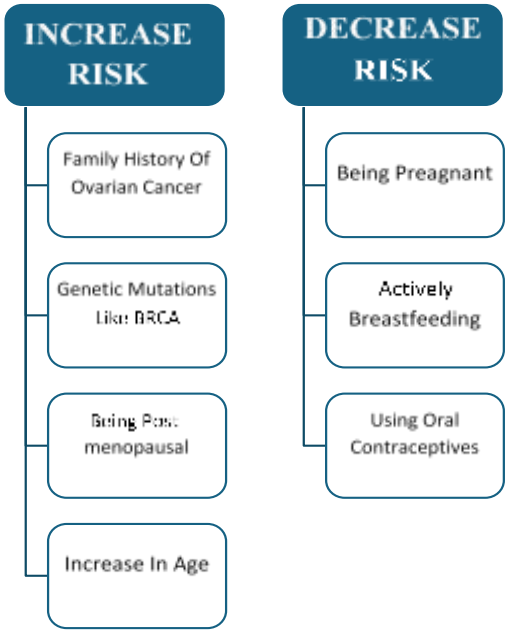


Figure 7: Risk factors of ovarian cancer

- **Genetic & Family History**

Inherited Gene Mutations: Changes in BRCA1, BRCA2, or genes linked to Lynch syndrome significantly increase risk. Family History: A mother, sister, or daughter with ovarian cancer raises your risk, especially if multiple close relatives are affected [63].

- **Reproductive & Hormonal Factors**

Never Pregnant: Women who have never given birth have a higher risk. Hormonal Changes: Starting periods early (before 12) or menopause late (after 55) increases risk. Infertility & Treatments: Unexplained infertility and multiple IVF cycles are linked to higher risk, while oral contraceptives are protective. Hormone Replacement Therapy (HRT): Postmenopausal HRT use can increase risk [64].

- **Lifestyle & Other Factors**

Age: Risk rises with age, especially after 50-60. Obesity: Being overweight or obese increases risk, particularly postmenopause. Smoking: Linked to increased risk, particularly for mucinous ovarian cancer. Endometriosis: A history of this painful disorder raises risk [65].

- **Protective Factors (Reduce Risk)**

Pregnancy: Having children, especially earlier in life. Oral Contraceptives (Birth Control Pills): Known to reduce risk. Tubal Ligation/Hysterectomy: May also lower risk [66].

Prevention of Ovarian Cancer

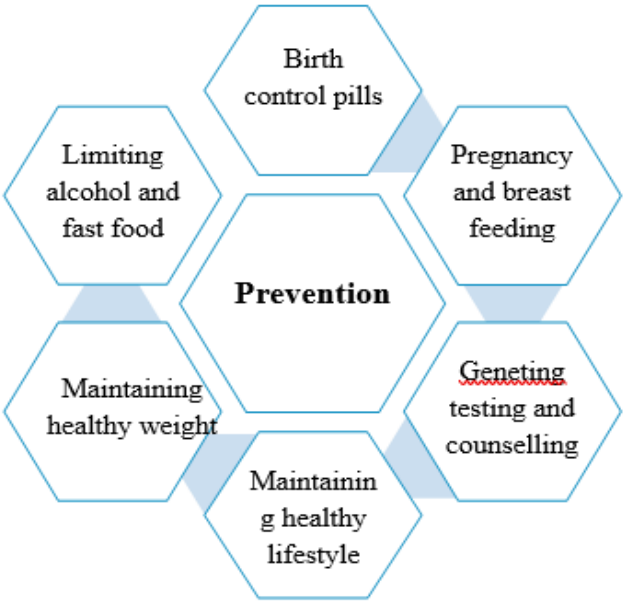


Figure 8: Prevention of ovarian cancer

Surgical Technique of Ovarian Cancer

1. **Surgery to remove the womb, ovaries and fallopian tube**

Your surgeon needs to make sure that they remove as much cancer as possible. So, most women have surgery to remove: both ovaries the fallopian tubes the womb, including the cervix This operation is called a total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) [67]. Having children in the future: -For some low-grade stage 1A cancers, it might be possible to remove the affected ovary and fallopian tube. The unaffected ovary and your womb are not removed [68]. This means you might be able to become pregnant and have a baby afterwards.

2. **Cytoreductive surgery**

The aim of cytoreductive surgery is to remove as much of the cancer as possible if it has spread to other areas in your pelvis or abdomen. This is sometimes called debulking surgery. You may have cytoreductive surgery if your cancer is stage 2, 3 or 4. Your surgeon removes your ovaries, fallopian tubes, womb and cervix. They also try to remove other tissue in the pelvis or abdomen that they think might be cancer. You have chemotherapy into your vein (intravenously) after cytoreductive surgery. The less cancer there is after surgery, the easier it is for chemotherapy to kill the remaining cancer cells. You might have chemotherapy intravenously before and after surgery. This is called interval cytoreductive surgery [69].

3. **Hyperthermic intraperitoneal chemotherapy [HIPEC]**

If you have interval cytoreductive surgery, your surgeon might suggest you also have a treatment called hyperthermic intraperitoneal chemotherapy (HIPEC). You have this as part of your operation. HIPEC treatment means having warm chemotherapy pumped into your abdominal cavity. [70] They usually use a chemotherapy drug called cisplatin. It aims to kill any remaining cancer cells. Once the surgeon has removed the cancer, they put some small plastic tubes (drains) into your abdomen. These are connected to a special HIPEC machine. The HIPEC machine warms the chemotherapy and pumps it around your abdomen. The chemotherapy stays in your abdomen for around 90 minutes. It is then drained back out of the abdomen into a drainage bag outside of your body [71].

4. Bowel surgery

Sometimes surgeons have to remove part of your bowel if the cancer has spread there. They may have to create an opening (stoma) on the outside of the abdomen for bowel movements to come out into a bag. This is called a colostomy. A stoma is often only temporary. The surgeon can do a smaller operation to close the stoma up again. This happens once everything has settled down from your first operation [72].

5. Historectomy

A total hysterectomy removes all of the uterus, including the cervix. The ovaries and the fallopian tubes may or may not be removed. This is the most common type of hysterectomy. A partial, also called subtotal or supracervical, hysterectomy removes just the upper part of the uterus. Cancer (or precancer) of the uterus, ovary, cervix, or endometrium (the lining of the uterus). Hysterectomy may be the best option if you have cancer in one of these areas. Other treatment options may include chemotherapy and radiation [73].

Complications of Ovarian Cancer

A rare complication of adnexiectomy, which occurs particularly when surgery is made difficult by the presence of extensive peri-adnexial adhesions, is the per- sisting presence of a thin segment of ovarian tissue, call- ed the ovarian remnant syndrome [74]; this may cause the onset of delayed pelvic pain, the re-appearance of adnexial growths, dyspareunia, and urethral compression [74].

CONCLUSION

Ovarian cancer remains a significant cause of morbidity and mortality globally with rising rates in many low- and middle-income countries and increasing case numbers in high income countries because of population aging. Five-year relative survival is below 45% and, unlike other common cancer types, the proportion of women who die from their disease has not improved substantially over time. We discussed about the early diagnosis and prevention of the ovarian cancer the diagnosis like transvaginal sonography is safe, time efficient, and well tolerated by patients. Transvaginal sonography screening for ovarian cancer is associated with a high sensitivity and a moderate specificity. The cost of TVS screening is reasonable and is equivalent to that reported for other screening tests. Although the hope remains that a combination of serum markers will be effective in ovarian cancer screening, the lack of sensitivity of serum CA 125 and its inability to lower stage at detection has limited its usefulness as a screening method. After diagnosed the tumor we have the options of surgery like historectomy, bowel surgery, cytoreductive surgery, HIPEC are the surgery to remove womb, ovary, fallopian tube. Therefore, improving awareness of early symptoms, identifying high-risk women, and integrating advanced diagnostic tools are essential to reduce ovarian cancer–related mortality. Multidisciplinary management involving gynecologic oncologists, radiologists, and pharmacists plays a crucial role in optimizing treatment outcomes. Recent advances in targeted therapy and maintenance treatment have shown promise in prolonging survival. Therefore, continued research, early detection strategies, and patient-centered care are key to improving prognosis and quality of life in ovarian cancer patients.

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