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*Review Article*

# Role of Preventive Oncology in Ovarian Cancer

Alka B Patil[1], Amruta Ahirrao[2], Lavanya Anuranjani[2]

[1]Professor & HOD, Dept. of Obst. & Gynec, ACPM Medical College, Dhule
[2]Resident, Obst. & Gynec, ACPM Medical College, Dhule, Maharashtra, India.

Corresponding Author: Alka B Patil

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## ABSTRACT

Ovarian cancer is a major cause of mortality from malignancies. A late diagnosis may be a major contributing factor in the overall poor prognosis. Finding the appropriate screening strategy for ovarian cancer remains a challenge. Difficulties with ovarian cancer screening are discussed. The risk factors for ovarian cancer are highlighted. Various screening methods are investigated. The three screening techniques available at this time (pelvic examination, CA-125 level & vaginal ultrasound) are reviewed. As there is no effective screening method, efforts should be directed towards preventive measures. Possible future directions in diagnosis of ovarian cancer are captured.

***Key words:*** preventive oncology, ovarian cancer, CA-125, risk factors.

## INTRODUCTION

***To cure was the voice of the past, to prevent is the divine whisper of today***

Ovarian cancer is a major cause of mortality from malignancies in developed countries. Ovarian cancers have vague symptoms such as abdominal discomfort or bloating, and therefore the majority of the cases present at an advanced stage. A late diagnosis may be a major contributing factor in the overall poor prognosis. Stage I disease gives a relatively good 5-year survival of 85%, but this falls to about 15–30% for stage III and IV disease. Hence, ovarian screening has been proposed in order to improve early diagnosis of the disease and overall outcome. [(1)]

In this article, we review difficulties with ovarian cancer screening. We discuss various screening methods for ovarian cancer. We also emphasize preventive measures for ovarian malignancy. We capture possible future directions.

The common theme of the treatment modalities in ovarian cancer is loss of reproductive function , often with castration and associated morbidity and mortality. These treatments can be financially, emotionally and sexually threatening. The concept of preventive oncology has been developed to approach the cancer problem at various points in evolution with the overall goal of reducing cancer suffering and death. At the present time, cancer prevention involves determining the causes of cancer (Risk determinants), associated with the development of disease by epidemio-

logical studies (Risk factors). Avoiding or reducing exposure to risk determinants would result in a reduction of cancer risk.

A shift from treatment to prevention of the three major Gynecologic cancer is overdue. The traditional approach to cervical , endometrial and ovarian cancers had been secondary to tertiary prevention - early detection and treatment or mitigation of damage, respectively.

Although women have a range of practical , effective measures available to reduce their risk of these cancers, few are aware of them . Without this information women cannot make fully informed decisions about their health.

The challenges in cancer prevention for primary care health professionals are to apply effectively and efficiently the technologies that prevent disease occurrence and progression. The opportunity for providing preventive services in medical care would require consideration of economical, organizational, and conceptual barriers. [(2)]

***Difficulties with Ovarian Cancer Screening***

There are several intrinsic problems that render ovarian cancer screening difficult. Unlike cervical cancer, ovarian cancer appears to be a heterogeneous group in which there is no well-defined precursor lesion and the rate of disease progression can be highly variable. This contributes to the difficulty of finding an effective screening test that can detect early disease and hence improve survival. Furthermore, unlike in cervical cancer screening in which a positive smear can be further investigated by colposcopy and biopsy, and precursor lesions, such as cervical intraepithelial neoplasia, can be treated by a minor procedure such as a large loop excision of the transformation zone, a positive test for ovarian screening would lead to a surgical intervention, e.g. Diagnostic laparoscopy and bilateral salpingo-oophorectomy, with its potential surgical complications. This further adds to the importance of finding a highly specific test. A screening test with 100% sensitivity and 99.6% specificity would still subject 10 women to surgery for each case of malignancy established. [(1)]

***Risk factors of ovarian cancer***

- Age > 40 years
- Endocrinal factors
- Infertility
- Nulliparity
- Late menopause
- Personal or family history of ovarian cancer
- Personal or family history of breast, colon, or endometrial cancer
- Hereditary ovarian cancer syndromes:
  -Breast –ovarian cancer syndrome
  -Site-specific ovarian cancer syndrome
  -Lynch II syndrome
- Frequent miscarriages
- Use of ovulation-inducing drugs (eg. clomiphene)
- Environmental factors:
  -High –fat diet
  -Lactose intake in subjects with low tissue levels of galactose-1-phosphate uridyl transferase
- Endometriosis [(3)]
- Patients who have had radiation to the ovaries for menorrhagia
- Patients of higher socio economic status
- White women are at higher risk
- Blood group A [(4)]
- Some studies have shown that postmenopausal women taking estrogen may be at increased risk for developing ovarian cancer [(5)]

***Reduced risk has been noted in following-***

- In long term contraceptive pill users

- Multiparous patients
- Patients who breast feed
- Patients of lower socioeconomic status
- Japanese, Hispanic, Chinese and black woman [(4)]

Use of combination oral contraceptives for a decade reduces a woman's risk of ovarian cancer by about 80 percent. Two principal theories have been cited to explain this protection.

1)One holds that each ovulation exposes the ovarian epithelium to a finite risk of malignant transformation over a lifetime. "Incessant ovulation "could lead cumulatively to an increased risk of cancer.

2) Alternative hypothesis is that oral contraceptives protect by suppressing gonadotropins.

The protection afforded by tubal sterilization may be due to isolation of the ovaries from carcinogens from external environment . The reproductive tract delivers external agents to the peritoneal cavity. Vasectomy does not confer this important protection. Hysterectomy also protects against ovarian cancer, although apparently to a lesser extent. [(2)]

An optimal screening test has high sensitivity, specificity, patient acceptance and is easy to perform. The three screening techniques available at this time (pelvic examination, CA-125 level and vaginal ultrasound) do not actually diagnose ovarian cancer but only suggest its presence; laparotomy is required for definitive diagnosis. [(6)]

***Bimanual Pelvic Examination:-***

Main advantage of pelvic examination as a screening test is:

- It's relatively low cost
- Ease with which it is performed
- Non requirement of specialized equipment

But this does not have sensitivity or specificity. Early stages are rarely detected due to the deeper anatomic location of the ovary. The diameter of normal post-menopausal ovary is 2x1x0.5cm rendering it impalpable on bimanual physical examination. Any palpable ovary in a woman more than 3-5 years after menopause must be considered pathological and is an indication for prompt investigation. Cases, in which tumours were detected by pelvic examination, are usually in advanced stage and are associated with poor prognosis. Annual pelvic examination with careful palpation of both ovaries is an essential component of ovarian cancer diagnosis. [(7)]

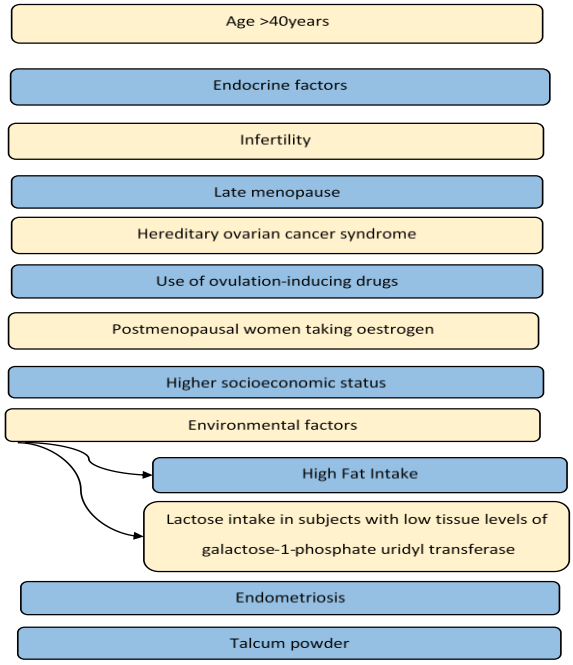


**Figure 1: Risk Factors for Ovarian Cancer**

Bimanual pelvic exam – Is the only cost effective means currently available and pelvic exam should be performed at any opportunity like antenatal booking visit, postnatal visit, cervical cancer screening. [(8)]

The most frequent symptoms are abdominal discomfort or vague pain, abdominal fullness, bowel habit changes,

early satiety, dyspepsia and bloating. The presence of a pelvic mass at clinical evaluation is an important sign of possible ovarian cancer. Occasionally, patients may present with bowel obstruction due to intra-abdominal masses or shortness of breath due to pleural effusion. In early stage disease, the patient may complain of irregular menses if she is premenopausal; if a pelvic mass is compressing the bladder or rectum, the patient may report urinary frequency and/or constipation. In advanced stage disease, patients most often have symptoms related to ascites and abdominal distension due to masses. [(9)]

Physicians evaluating women with this constellation of symptoms must be cognizant of the possibility of the ovarian pathology may be causing these symptoms. However, some evidence suggests that the screening tests using these symptoms is not as sensitive or specific as necessary, especially in those with early stage disease. [(10)]

Tumor-associated antigens released into the circulation have been described in many diseases. Ideally, a tumor marker should be able to detect subclinical disease (i.e. Screening).Bast and colleagues in 1981 first described CA125, a 200 kd glycoprotein recognized by the murine monoclonal antibody CA 125 as a marker for epithelial malignancies A raised level of antigen was detectable in the serum of 82% of women with epithelial ovarian cancer but in only 1% of healthy blood donors Epithelial ovarian cancers with low or normal levels of CA125 are usually mucinous tumors. The antigen is not specific to ovarian cancer as raised serum levels may also be found in 29% of other cancers (lung, breast, pancreas, and colorectal) and in 6% of women with nonmalignant conditions such as cirrhosis with ascites, acute pancreatitis, ovarian cysts, endometriosis, and pelvic inflammatory disease.

Serum CA125 measurement in healthy women has been used as a means of selecting women for ultrasonography. This increases the specificity of examination, but the predictive value of screening is about 10%. At this level, a significant number of surgical explorations would be performed for nonmalignant ovarian pathology. Furthermore, it is not clear how often patients should have examinations repeated, as some of the patients with normal CA125 at screening subsequently developed ovarian cancer on follow-up. Currently, the combination of CA125 and transvaginal color doppler studies is likely to be the most successful screening tool, particularly if applied to women with a strong family history of ovarian cancer, as they have a higher risk of developing the disease. [(11)]

### *Possible Screening Tests CA 125*

Since CA 125 levels in women without ovarian cancer would remain normal while those in women with cancer would rise. Assessment of serial CA 125 in an individual using a 'risk of ovarian algorithm', which takes into account the rate of change and age instead of a single cut-off value, may improve the performance of the test. [(1)]

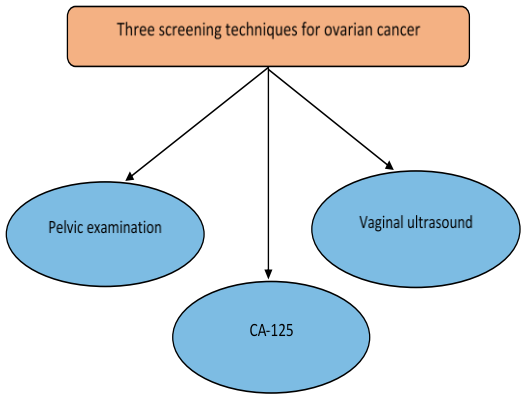


**Figure 2: Three Screening techniques for ovarian cancer**

### *Nonepithelial Ovarian Cancer*

α-fetoprotein and human β chorionic gonadotrophinare probably the best known tumor markers in clinical practice and are invaluable in the diagnosis, treatment, and follow-up of ovarian germ cell tumors. Serum placental alkaline phosphatase and lactate dehydrogenase are also sometimes helpful as markers of dysgerminoma. Traditionally, stromal tumors produce estradiol, and this has been used as a biochemical tumor marker. Granulosa cell tumors - a subgroup of stromal tumors, causing approximately 2% of ovarian malignancies - have been demonstrated to produce both Estradiol and Inhibin. Approximately 30% of granulosa cell tumors and most extraovarian recurrences do not produce estradiol. Inhibin is a hormone produced by the granulosa cells of the ovary. It is a glycoprotein consisting of two subunits—β and α. A new radioimmunoassay has now been developed which recognizes both subunits of Inhibin and is more sensitive. Serum levels of Inhibin have been demonstrated to correlate closely with clinical disease and, like CA125, can predict relapse. [(11)]

***New Biomarkers***

Apart from CA 125, a number of other biomarkers have been identified to be associated with the development of ovarian cancers. The human epididymis protein 4 (HE4) is one of the most promising new serum biomarkers. It was reported to be expressed in 32% of ovarian cancers without elevated CA 125 expression. [(18)] HE4 in combination with CA 125 could better differentiate malignant ovarian masses from benign ones, and HE4 has been reported to outperform CA 125 as a first-line screen owing to its high sensitivity. Further studies are needed to investigate whether multimodal screening with TVS and a biomarker algorithm incorporating CA 125 and HE4 would improve on the current screening methods. [(1)]

The SGO (society of gynecologic oncology) has stated that additional research is necessary to validate the ovasure screening test before making it available outside of a clinical trial.

Ovasure test uses 6 biomarkers:-

- Leptin
- Prolactin
- Ostopontin
- Insulin like growth factors
- Macrophage inhibitory factor
- Ca 125

Recent data shows that several markers (including Ca 125, HE4, mesothelin, decoy receptor 3(DCR 3), and sporadin-2) do not increase early enough to be useful in detecting early stage ovarian cancer. [(10)]

***US Imaging***

Transvaginal US, Transabdominal US, or both are considered the first-line imaging tool whenever an ovarian lesion is suspected. Currently, US is also the main triage pretreatment imaging modality for this disease. . It allows real-time evaluation of the region of interest, including functional information on tissue vascularity. The lack of radiation is particularly advantageous when imaging the pelvic region, especially in younger patients. In addition, US is also less expensive than MR imaging or CT.

Unfortunately, even with the help of scoring systems, the sensitivity and especially the specificity ranges of US for the detection and classification of ovarian lesions are usually too low to allow the application of US as a first-line screening tool in the general population. [(12)]

***USG:*** Discrimination between benign and malignant lesions of the ovary can be made on the basis of USG patterns. Anechoic lesions have a high likelihood of being benign. As the percentage of echogenic material in cyst increases the likelihood of malignancy increases. Benign lesions are likely to be unilateral, unilocular and thin

walled with no papillae or solid areas. Septae if present in benign masses are also thin. In contrast, malignant lesions are often multilocular with thick walls, thick septae and mixed echogenicity due to presence of solid areas.

Other signs suggestive of malignancy include-

- Presence of irregular solid parts within the mass
- Indefinite margins, Papillary projections extending from inner wall of the cyst
- Presence of ascites
- Hydronephrosis
- Pleural effusion
- Matted bowel loops
- Omental implants
- Lymphadenopathy

Size of the tumour may also give clues regarding the nature of the mass. Larger tumours usually greater than 8 cm in size have been thought to be associated with high risk of malignancy in comparison to smaller ones. Palpable ovary in post-menopausal woman must be considered significant finding. [13]

The framework of the IOTA (International OvarianTumour Analysis) Study simple ultrasound based rules were developed to correctly classify as benign or malignant adnexal tumors.

They selected five simple rules to predict malignancy (M-rules):

(1) Irregular solid tumor;

(2) Ascites

(3) At least four papillary structures

(4) Irregular multilocular solid tumor with a largest diameter of at least 10cm

(5) Very high color content on color Doppler

Five simple rules to suggest a benign tumor (B-rules)

(1) Unilocular cyst

(2) Presence of solid components where the largest solid component is < 7 mm in largest diameter

3) Acoustic shadows

4) Smooth multilocular tumor less than 10 cm in largest diameter

(5) No detectable blood flow on Doppler examination [14]

***Colourflow Doppler***

In diagnostic approach, next to ultrasound, colourflow Doppler is useful for distinguishing between benign and potentially malignant lesions. The rationale of the use of color Doppler is related to the fact that during the fast growth, the tumor spread through the neo-angiogenesis, characterized by a poor smooth muscular component: blood flow resistance in these vessels is less than that found out in vessel with normal wall components. Color/power Doppler study of an ovarian mass enables to identify also small size vessel, characterized by slow flow and to define appearance, distribution and architecture. [14]

***CT Imaging***

CT imaging is not a primary imaging tool in the early diagnosis of ovarian cancer. CT offers much lower inherent tissue contrast than does MR imaging, even with the use of contrast agents. Other disadvantages of CT include a higher risk of adverse events due to the use of iodinated contrast agents and ionizing radiation, which is especially undesirable in premenopausal women and is also suboptimal in a screening setting where repeated imaging is required.

***MR Imaging***

MR imaging offers several advantages in the imaging of the pelvis. It does not require the use of ionizing radiation; there is no substantial operator dependency; and there are a number of generally well-tolerated contrast agents available. Differentiation of benign and malignant tumours with MR imaging is based on primary morphological criteria of

the tumour structure comparable to the criteria for USG.

The cost intensiveness of MR imaging, on the one hand, renders it a less suitable modality for screening in the general population. It's relatively good performance in lesion characterization as well as in staging, on the other hand, makes it a valuable secondary diagnostic tool in a selected high-risk population if further preoperative imaging is required. [(14)]

The American Society of Clinical Oncology has affirmed the role of clinical oncologists in identifying and managing patients with familial cancer risk. Inherited mutations in the genes ***BRCA1*** and ***BRCA2*** are responsible for the majority of hereditary breast and ovarian cancers, and these mutations also increase the risk of second cancers in women already diagnosed with breast malignancy. Options for women with inherited mutations in ***BRCA1*** and ***BRCA2*** include surveillance, chemoprevention and prophylactic surgery, which must be considered separately for the management of the risk of breast cancer and of ovarian cancer. Knowledge of the hallmarks of hereditary risk, options for medical intervention, possible results of ***BRCA1*** and ***BRCA2*** laboratory analysis and the psychological concerns of patients about hereditary risk evaluation enables oncologists and other health care providers to effectively counsel and manage women with hereditary risk of breast and ovarian cancer.

A woman inherits a mutation in ***BRCA1*** and ***BRCA2*** from one of her parents; de novo germline mutations (which usually occur during spermatogenesis) are thought to be rare in these genes. By definition, such mutations cannot be acquired after birth. Accordingly, tests for mutations in ***BRCA1*** and ***BRCA2*** are normally performed only once in a person's lifetime.

Individuals who carry a mutation in ***BRCA1*** or ***BRCA2*** have one normal copy of each gene in addition to one mutated copy. Each offspring of a man or woman who carries a mutation has an equal chance of inheriting the normal copy as the mutated copy. Offspring who inherit the mutated gene are at a greatly increased risk of breast and ovarian cancer, whereas offspring who inherit the normal copy from their parent are not at increased risk even if their parent developed breast or ovarian cancer. Thus, mutations in ***BRCA1*** and ***BRCA2*** confer cancer risk as an autosomal dominant trait, with offspring having exactly a 50% chance of being at greatly increased risk of cancer or of being at the general population risk.

***BRCA1 and BRCA2 Mutations and the Risk of Ovarian Carcinoma***

The risks of ovarian carcinoma conferred by mutations in ***BRCA1*** appear to be higher than for ***BRCA2***. Mutations in ***BRCA1*** are associated with a risk of ovarian carcinoma estimated between 28% and 44% by age 70 (compared with the general population risk of 1.8%). The risk of ovarian carcinoma by age 70 for most ***BRCA2*** mutations is currently estimated to be 27% which represents a 15-fold increase over that of the general population. Most ovarian carcinomas associated with mutations in ***BRCA2*** appear to occur after age 50.

***Interventions That Address the Increased Risk of Ovarian Cancer***

Oral contraceptive use may reduce the risk of ovarian cancer in women with pathogenic mutations in ***BRCA1*** and ***BRCA2***. A recent retrospective, multicenter, case-control study of 207 women with hereditary ovarian cancer (using their sisters as controls) found that the use of oral contraceptives for six or more years was associated with a 60% reduction in the risk of ovarian cancer. Adjusting for parity, the presence or absence of a tubal ligation and ages at the delivery of a first or last child did

not influence the protective effect of oral contraceptive use. While oral contraceptive use has been associated in some studies with a small increase in the risk of breast cancer, the authors observed no difference in the history of oral contraceptive use between women who had had breast cancer and those who had not and other evidence also challenges whether the risk of breast cancer is increased by the use of oral contraceptives. [15]

***Prophylaxis for ovarian malignancies:***

As there is no effective screening effort should be directed towards preventive measures

- Investigate all solid adnexal masses or bilateral cystic masses or adnexal cysts >10cm.
- Investigate all post-menopausal women with palpable ovaries.
- It is advisable to remove both ovaries when hysterectomy is done for benign indications in perimenopausal women.
- In patients showing adenomatous hyperplasia investigate serum estrogen level before hysterectomy (with ovarian conservation) and 3 weeks later. If it shows elevation of E3 levels on two consecutive occasions, ovarian neoplasm should be suspected.
- Role of laparoscopy: when ovaries are enlarged and appear suspicious, peritoneal fluid can be aspirated through the scope and subjected to cytology for easy diagnosis [16]
- Breast feeding reduces the incidence of ovarian cancer and should be encouraged
- Oral contraceptive use significantly protects against ovarian cancer and protection is proportional to duration of use and lasts 10-15 years after cessation of use.
- Avoid indiscriminate use of ovulation induction agents. Rossing et al, reported relative risk of 11.1 in women who have taken clomiphene for more than a year. However, no increase was reported in women undergoing IVF cycles suggesting that risk are related to duration of use. [8]

***Prophylactic BSO***

Prophylactic BSO is widely considered the most effective strategy reducing the risk of ovarian cancer in BRCA carries. In general, it is a relatively low-risk surgical procedure that often can be performed laparoscopically.

The timing of prophylactic surgery needs to be individualized for each patient. Many women are torn between the conflicting goals of cancer prevention and childbearing. Although epithelial ovarian cancers have been reported in BRCA carriers in their twenties, the risk of hereditary ovarian cancer does not rise sharply until the late thirties for BRCA1 carriers and the late fifties for women who have BRCA2 mutations. This knowledge has led to the current practice of recommending prophylactic BSO at the completion of childbearing. Negative effects of this aggressive risk reduction strategy include surgical menopause, with the attendant increased risk of cardiovascular disease, vasomotor symptoms, and bone loss.

Appropriate steps in a risk-reducing bilateral salpingo-oophorectomy:

- Carefully survey all abdominal organ and peritoneal surfaces.
- Perform abdomino pelvic wash with saline and send for cytological evaluation.
- Biopsy any suspicious nodule and send them for immediate frozen pathologic evaluation.

- Transect the ovarian vessels at least 2cm proximal to the ovary.
- Excise the entire ovary and fallopian tube, transecting the tube as close as possible to its insertion into the cornu.
- Remove the specimens intact and communicate the nature of the surgery explicitly with the consulting pathologist so that appropriate processing of the specimens occurs.
- If at any time in these steps a malignancy is encountered, immediate consultation with a gynecologic oncologist is ideal.

Recommendations for hysterectomy as part of risk reducing surgery in BRCA mutation carrier remain controversial. Many patients elect to have the uterus removed when undergoing prophylactic BSO because they have completed their family or have other gynecologic indications for hysterectomy.

Screening of women at increased risk for ovarian cancer can be considered in those not wishing prophylactic surgery and typically should include a twice annual pelvic examination, serum CA-125 measurement and transvaginal sonography. [(1)]

## DISCUSSION

Currently, ACOG recommends that the best way to detect ovarian cancer is for both the patient and her clinician to have a high index of suspicion of the diagnosis on symptomatic women. The society of gynecologic oncologists also recognizes that most women with ovarian cancer are symptomatic, yet go undiagnosed for many months. A true assessment of the early detection potential of any test requires evaluation of its performance before the onset of symptoms and clinical diagnosis. Unfortunately, no currently available tests have been shown to reliably detect ovarian cancer in its earliest and most curable stages, and so educating women is essential.

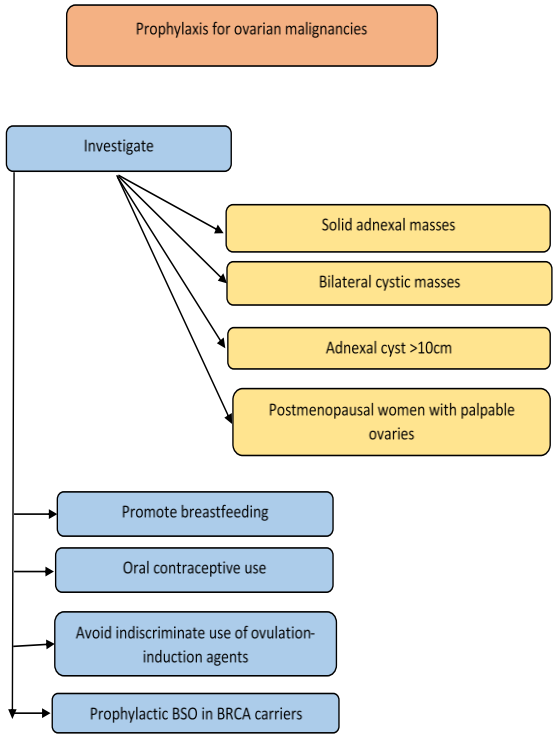


**Figure 3. Prophylaxis for ovarian malignancies.**

Historically, ovarian cancer was thought to be a "silent killer" because symptoms were not thought to develop until advanced stages when chances of cure were poor.

Ultimately, the timely diagnosis of ovarian cancer will rely on clinical judgment and careful analysis of presenting symptoms with the context of a thoughtful dialogue between the patient and her physician. Symptoms most typical of ovarian cancer include bloating, abdominal pain or pelvic pain, and difficulty in eating, urinary symptoms. Although most women who have these symptoms do not have ovarian cancer, it is important that provider include ovarian cancer in their differential diagnosis. Until there is a screening test, awareness is the best. [(18)]

Serological markers provide a means of monitoring tumor activity at many stages of the disease- diagnosis, therapy, and relapse. However, it is important that they are used appropriately and their significance is understood. Knowledge about raised levels of CA125 often raises questions as well as answers; we need to be able to make use of the information available. Early knowledge about relapse does not necessarily help outcome, as better therapies are needed. Progress in therapy is likely to come from a combination of better drugs and a greater understanding of the biology of the disease. Study of serological and tumor-related surface markers needs to continue. Markers for ovarian cancer, and, in particular, CA125, have led the way for epithelial tumors and provide a valuable model for further studies.

Finding the appropriate screening strategy for ovarian cancer remains a challenge. Refinement of the current available methods, together with the new biomarkers and proteomic techniques, may help to provide more effective screening tests. It is also important to define the most appropriate target population to be screened. A different strategy may be needed for populations with different risks. Lastly, ovarian cancer is a heterogeneous group of disease. Current screening methods are based on the assumption that the disease originates from the ovary and would progress gradually from an early to late stage and that screening can detect the early-stage disease and thus reduce mortality. However, there are a high proportion of aggressive ovarian tumours that present as high-stage, high-grade disease, and this is the group that the current screening strategies may fail to detect. Targeting the differences in carcinogenesis between the tumours with different biological behavior may allow new approaches, such as those based on molecular genetic markers, to be developed to detect these aggressive tumours, and this will have more impact on reducing mortality from this disease.

In summary, results from large randomized trials so far could not yet clearly demonstrate that the current screening methods could allow earlier detection of the disease, and information on mortality from the large trials are not yet available. Based on the current evidence, routine population based screening in asymptomatic women cannot yet be recommended.

- No ideal screening strategy has been established for ovarian cancer, and therefore routine screening cannot yet be recommended.
- CA 125 is raised in only 50% of early disease and is also raised in a number of benign conditions; therefore, using CA 125 alone as a screening test would not be sensitive or specific enough.
- Transvaginal ultrasound can effectively detect ovarian masses but cannot accurately assess the nature of the mass. TVS alone leads to a high number of unnecessary operations.
- A combination of serial CA 125 measurements and transvaginal ultrasound is the commonest screening strategy being investigated in large randomized trials.
- Combining CA 125 with transvaginal ultrasound may reduce the number of unnecessary surgeries.

A significant proportion of breast cancer patients diagnosed before age 50 developed their malignancy because of detectable mutations in ***BRCA1*** or ***BRCA2***. The increased risk of a contralateral breast cancer, as well as a subsequent carcinoma of the ovary, may warrant a specialized management strategy for these women. In addition, the identification of a mutation in ***BRCA1*** or ***BRCA2*** in a patient with or without cancer has implications for her relatives. The ability to diagnose hereditary

susceptibility to breast and ovarian cancer through genetic testing may provide opportunities for enhanced medical management of "at-risk" women. An oncologist should be able to assess a patient's personal and family history for the possibility of hereditary breast-ovarian cancer syndrome, understand the benefits and limitations of genetic tests for this condition, and accurately answer a patient's questions about the hereditary syndrome of breast and ovarian cancer. Fortunately, oncologists possess the training and experience to identify women with increased cancer risk and manage them appropriately. The use of genes rather than slides to identify such women, and the added implications of genetic tests for other relatives, may simply represent an extension of skills already possessed and utilized by oncologists who care for women with cancer.

The last decade has seen significant advances in the surgical, chemotherapeutic, and biologic therapies of ovarian cancer, and patient now are living longer and better. The reality for most patients, who have ovarian cancer, however remains an initial diagnosis of metastatic disease, a surgery with subsequent chemotherapy and possible remissions, recurrence and with growing chemoresistance, death from disease. Using the family history in combination with current molecular and genetic techniques, physicians now are better able to identify the mutations in high risk pedigrees.

The overall effect on Quality of life, including the risk of required invasive follow up procedures and induced costs of a false positive screening results, may best be balanced by implementation of a screening program in a population at increased risk of ovarian cancer. Challenge is that the majority of ovarian cancers occur in women without known risk factors. Identification of novel epidemiologic, genetic, or blood based markers of ovarian cancer risk is a critical research need.

Prevention of gynecologic cancer is a neglected area of woman's health care. Investments in prevention will lower the costs of diagnosis and treatment of these diseases . Health care providers and the media – must advice women of these opportunities. Without this information, women cannot make truly informed decisions about their health.

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