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Review Article

Role of prevention and screening in epithelial ovarian cancer

Peddireddi Reddi Rani^{1*}, Kanipakapatnam Sathyanarayana Reddy²

¹Department of Obstetrics & Gynaecology, ²Department of Radiation Oncology, Mahatma Gandhi Medical College & Research Institute, Pilliarkuppam, Puducherry 607 402, India

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*Correspondence:

Dr. Kanipakapatnam Sathyanarayana Reddy,

E-mail: satyare@hotmail.com

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ABSTRACT

Epithelial ovarian carcinoma is a disease with poor prognosis and high mortality among gynaecological cancers due to inaccessibility of ovary for inspection or sampling and lack of proper screening methods. Strategies to detect early ovarian cancer include estimation of serum CA-125 and transvaginal ultrasound (TVS) for morphological index. Studies have shown that screening of asymptomatic average risk post-menopausal women did not show any benefit and are associated with false positive results which may lead to unnecessary surgery and resultant morbidity. The risks outweigh benefits.

Present recommendation is to screen high risk women especially hereditary cancers and offer risk reducing surgery when needed. Prophylactic salpingectomy/oophorectomy may offer the opportunity to prevent ovarian cancer. More trials and more research in newer biomarkers are needed.

Keywords: Screening, Transvaginal ultrasound, CA-125, Risk reducing surgery

INTRODUCTION

Of all gynaecological malignancies ovarian cancer carries the worst prognosis and it is estimated to be the ninth most common cancer and fifth most common cancer related mortality. Most of them are diagnosed in advanced stages of III and IV with a five year survival rate of less than 28%. Only 15% of ovarian cancers are diagnosed in early stage with a five year survival rate of 94%.¹ This suggests that early detection will improve prognosis. Early diagnosis is often difficult due to lack of specific symptoms and also ovaries are inaccessible for direct inspection and palpation. Despite the significant disease burden ovarian cancer is relatively rare in general population with an estimated age adjusted incidence of 13 per 100,000 women.² The age standardized incidence rate (ASR) varies widely; as low as 0.06 per 100,000 in China to as high as 16.3 in Switzerland.³ In India during the period 2004-5 proportion of ovarian cancer varied from 1.7% to 8.7% of all cancers affecting women as reported

by various urban and rural population based cancer registries operating under the network of National Cancer Registry Programme of the Indian Council of Medical Research.⁴ Screening tests lack specificity and there is no single effective screening test for ovarian cancer. Main strategies for screening include biochemical markers and transvaginal ultrasound (TVS).

Screening

Low risk women

Use of tumour marker CA-125 and TVS has been evaluated for screening asymptomatic low risk women. These proved to be ineffective because of low prevalence of epithelial cancer which is reported to be approximately 1 case for 2,500 women per year. It is estimated that a test with 100% sensitivity and 99% specificity would have a positive predictive value of only 4.8% which means 20 out of 21 women undergoing surgery for suspected ovarian cancer will not have the disease.⁵

High risk women

The definite risk factor known to increase the risk of ovarian cancer include an identified BRCA gene mutation and a family history of cancer which is suggestive of ovarian cancer syndrome. Women with these conditions should be referred for genetic testing for proper assessment of the risk of developing ovarian cancer. Women with BRCA-1 mutation have a life time risk of 63% for developing ovarian cancer before the age of 70 years and breast cancer risk is 85%. Risk of developing ovarian and breast cancer are 27% and 84% respectively among women who show BRCA-2 mutations before the age of 70 years.⁶

Women with Lynch syndrome/hereditary non-polyposis colorectal cancer(HNPCC) caused by DNA mismatch repair genes carry the risk of developing endometrial cancer in 42-60%, ovarian cancer in 9-12% by the age of 70 years and also have 40-60% life time risk of developing colorectal cancer.⁷

The strongest known risk factor is a family history of the disease which is present in about 10-15% of women with ovarian cancer. Women with a single family member affected by epithelial ovarian cancer have a risk of 4-5%, while with two affected family members the risk is 7%. Women with hereditary ovarian cancer syndrome defined as having at least two first degree relatives with epithelial ovarian cancer have a life time probability as high as 13-55% to develop epithelial ovarian cancer.⁸

Other risk factors

1. Age- Incidence increases with age; median age at diagnosis is 63.
2. Obesity
3. Hormone replacement therapy (HRT)
4. Early menarche and late menopause
5. Endometriosis
6. Smoking
7. Association between ovulation induction and ovarian carcinoma Infertility alone is an independent risk factor. Nulliparous women have a higher risk of ovarian cancer irrespective of usage of fertility drugs. A 2013 Cochrane review concluded that there may be an increased risk of borderline ovarian tumours in sub-fertile women but no convincing evidence of increase in the risk of invasive epithelial ovarian cancer with fertility drug usage.⁹

Table 1: Summary of risk factors and protective factors by strength of evidence.¹⁰

| | Established risk factors | Possible risk factors | Suspected risk factors | Protective factors |
|---|---|-----------------------|------------------------|--------------------|
| 1 | Family history and BRCA mutation status | Early age at menarche | HRT | Lactation |

| | | | | |
|----|-------------|-----------------------|----------------------|------------------------------|
| 2. | Age | Late age at menopause | Obesity | Tubal ligation |
| 3. | Nulliparity | Infertility | Sedentary life style | Hysterectomy |
| 4. | | | Low vegetable intake | Oral contra-ceptive pill use |
| 5. | | | Cigarette smoking | Oophorectomy |

Screening methods

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 in symptomatic women.¹¹ But there are no tests that could reliably detect ovarian cancer in its earliest and most curable stage and so educating women and practitioners about symptoms and prompt initiating work up helps in timely diagnosis and treatment.

Symptoms and signs are usually present 3-6 months at least before diagnosis, these include increased distension or bloating, abdominal or pelvic pain, feeling full quickly or difficulty in eating etc. These symptoms and signs should be evaluated with suspicion of ovarian cancer, with pelvic examination, TVS and CA-125. Though a thorough bimanual pelvic examination is cost effective, it is not cost sensitive to detect ovarian cancer in asymptomatic women.

Tumour markers

CA-125 is the most extensively studied tumour marker in ovarian carcinoma. Ca-125 is a glycoprotein produced by majority of epithelial ovarian cancer (EOC). It is elevated in 61-95% of symptomatic patients with EOC and in 29-75% of those with stage I disease.¹² Normal value is 30-35 U/ml, it is influenced by menopausal status. In premenopausal women the sensitivity is decreased. It also can be elevated in other cancers like endometrial, breast, lung, lymphoma, colorectal cancer etc. It is also elevated in certain benign conditions like endometriosis, uterine leiomyoma, pregnancy, PID etc. It is not specific for ovarian cancer. In malignancy serial measurements show increase in value. Screening using a single CA-125 measurement is not specific with low sensitivity. Serial measurements combined with TVS improves sensitivity and specificity.

Trans vaginal sonography

It has been found to be safe and effective means visualizing ovaries. The earlier studies mainly focused on ovarian volume, normal premenopausal ovarian volume established to be >20 ml and for post menopausal women the cut off value is 8-10 ml. Risk Malignancy Index (RMI) is the most widely used index to diagnose ovarian cancer in suspected cases. It combines three pre-surgical features: serum CA-125, menopausal status (M) and Ultrasound score (U).

RMI: $U \times M \times CA-125$

U: One point for each of these morphological criteria-multilocular cysts, solid areas, bilateral lesion, metastases, ascites

M: Menopausal status is scored as 1 for premenopausal and 3 for postmenopausal status.

RMI score of 200 indicates high degree of suspicion of ovarian malignancy, sensitivity of 78% and specificity of 87%.¹³

Table 2: Morphological criteria of USG from TOTA group as benign and malignant has a sensitivity of 95% and specificity of 91%.¹⁴

| Benign Features | Malignant features |
|--|---|
| Unilocular cysts | Irregular solid tumour |
| Presence of solid component is <7 mm | Atleast four papillary structures |
| Presence of acoustic shadowing | |
| Smooth multiloculated tumour with largest tumour size < 100 mm | Irregular multilocular solid tumour with largest diameter ≥ 100 mm |
| No blood flow | Very strong blood flow |

The routine use of CT/MRI for assessment of ovarian masses does not improve sensitivity and specificity obtained by TVS in the detection of ovarian malignancies. What is needed is a multimodal screening using CA-125 and ultrasound. Patient should be referred to a specialist if four or more of the following indicators are present.¹⁵

1. Premenopausal (< 50 Years)
 - A. CA-125 > 200 U/ml
 - B. Ascites
 - C. Evidence of abdominal/distant metastases by scan or imaging studies.
 - D. Family history of breast or ovarian carcinoma (first degree relatives)
2. Post menopausal women (≥ 50 years)
 - A. Elevated CA-125 > 35 U/ml
 - B. Ascites
 - C. Nodular or fixed pelvic mass
 - D. Abdominal or distant metastases
 - E. Family history of breast or ovarian carcinoma (first degree relatives)

Biomarkers in ovarian carcinoma

Apart from CA-125, other biomarkers which may lead to early detection ovarian cancer HE-4 transthyretin, CA-15-3 and CA 72-4 were evaluated using specimens assembled from multiple cohort randomized trials including PLCO trial. Phase II and phase III biomarker studies concluded that CA-125 remained the “single best biomarker” for ovarian cancer.¹⁶

Moore et al¹⁷ evaluated proteomic biomarkers which include apolipoprotein a-1, truncated transthyretin, transferrin, hepcidin, beta-2 microglobulin, connective tissue activating protein III and interalpha-trypsin inhibitor heavy chain in addition to CA-125 and concluded that addition of these seven proteins did not improve sensitivity beyond the use of CA-125 levels alone.

Yushan Cheng et al¹⁸ found retinol binding protein-4 (RBP-4) found to be a potential biomarker in screening for ovarian cancer. They found concentrations of this biomarker was much higher (mean 89.13 ± 1.67 ng/ml) in ovarian cancer patients compared to healthy women (mean 10.85 ± 2.38 ng/ml).

Challenges in developing screening strategies in ovarian cancer:

1. No definite preinvasive or precursor lesion
2. Ovary is not accessible like cervix for direct inspection and sampling
3. Risk of false positives in ovarian cancer screening is a setback.

There is low prevalence of ovarian carcinoma. Incidence in women > 50 years it is 40 per 100,000 women. One needs to screen 2500 women to detect a single case of ovarian cancer and also requires invasive procedures like laparoscopy/ laparotomy.¹⁹ Current screening tests cannot detect ovarian cancer early enough to alter the natural history of the disease. Low prevalence affects sensitivity and specificity.

The ACOG recommends against screening for ovarian cancer in general population. The U.S. Preventive services task force gives ovarian cancer screening a grade ‘D’ recommendation, which indicates that women are harmed with false positive results than helped by early detection and hence it should be eliminated from a periodic health examination. It gives a grade ‘B’ recommendation for genetic counseling and testing of women with a pedigree consistent with a familial mutation that would increase the risk of ovary and other malignancies offering risk-reducing surgery dramatically lowers the risk of developing ovarian, fallopian tube or primary peritoneal cancer.²⁰

Harms of screening

PLCO trial (Prostate, lung, colorectal and ovarian cancer trial) provides the most reliable data to date on ovarian screening related harms.²¹ This is a large prospective randomized screening trial; 78,232 women in age group of 55-74 years were randomly assigned to screening who underwent annual TVS for 4 years and annual CA-125 for 6 years. Controls were women who were assigned for routine care. Median follow up of participants was 12.4 years. Ovarian cancer was diagnosed in 212 women in the screened group and 176 in the control group. There were 118 deaths caused by ovarian cancer in screened

group compared to 100 deaths among controls. Screening with annual TVS and CA-125 did not reduce the ovarian cancer mortality. Of the 3285 women with false positive result, 1080 underwent surgery and 163 (15%) experienced at least one serious complication. This confirms that ovarian cancer screening in asymptomatic low risk women can lead to unintended harm. Major complications with diagnostic procedures among women diagnosed with ovarian cancer included bowel injury, infections, blood loss and cardio vascular events.

US Preventive services task force (USPSTF)²² concluded that screening asymptomatic women for ovarian cancer via USG, serum tumour markers was not recommended. There was fair evidence that screening by CA-125, and TVS resulted in detection of ovarian cancer at an earlier stage but there was also evidence that impact on survival was small and that the potential harms of invasive testing might outweigh potential benefits. It did not decrease the cancer specific or overall mortality compared with usual care. There were potential harms associated with false positive screening test results, unnecessary surgeries and associated complications. There is no evidence for routine screening in average risk asymptomatic women.

UK Collaborative trial of ovarian cancer screening (UKCTOCS)²³ is a randomized controlled trial of 202,638 post menopausal women aged 50-74 years who were randomized into three groups. First group had annual screening with CA-125 testing, if abnormal followed up with TVS (multi modal screening group MMS), the second group had screening with TVS annually (USS) and the third group did not have any screening. Abnormal screening test results were repeated; if abnormality persisted they were evaluated and treated. The number of cancer cases detected were similar; 42 in MMS group and 45 in USS group. More borderline tumours were detected in USS group 20 vs 8 in MMS group. There was significant difference in specificity but not in sensitivity between the MMS and USS group for both ovarian and tubal carcinoma. Overall 48.3% of invasive cancer cases were early stage I or II with no significant stage distribution difference the two groups. Primary study results on mortality and other parameters from UKCTOS are awaited by late 2015. This may provide information on the complicated screening algorithms. The high proportion of early stage tumours detected is encouraging.

Preventive or risk reducing factors

Risk reducing surgery for women at high risk of developing epithelial ovarian cancer

The life time risk of ovarian cancer in the general population is 1.4% to 1.7% and in women

With hereditary ovarian cancer syndromes the risk is as high as 25-60%. It is important to identify the cancers caused by an inherited predisposition in the light of

prognostic implications for individuals and their families. Genetic risk assessment in these patients helps to provide individualized evaluation of the likelihood of having one of these gynaecologic cancers and also to provide tailored screening and preventing strategies such as surveillance, chemoprevention and prophylactic surgery which may reduce morbidity and mortality. Strategies that improve the outcome are breast cancer screening by MRI, colorectal cancer screening by colonoscopy, annual screening for ovarian cancer by CA-125 and TVS and offering prophylactic surgery. These procedures reduce the risk of ovarian cancer by 96% and breast cancer by 53% in women with BRCA-1 and BRCA-2 mutation.²⁴

Table 3: Guidelines for the management of women at increased risk of epithelial ovarian cancer.²⁵

| Risk of Ovarian Cancer | Suggested Management |
|---|---|
| 1. Increased risk | |
| Positive family history Single member affected Not suggestive of a hereditary cancer syndrome Risk of ovarian cancer 4-5% (Risk in general population 1.7%) | No evidence to support screening in this group Can consider risk reducing bilateral salpingo oophorectomy (BSO) based on individual considerations |
| 2. High risk | |
| Family history suggestive of Hereditary cancer syndrome Risk of ovarian cancer-13-50% | No evidence to support screening in this group Offer risk reducing surgery Screening to those who decline surgery |
| BRCA-1 mutation has a life time risk of ovarian cancer 35-46% | Offer risk reducing surgery (BSO) after the age of 35 years when child bearing is complete. |
| BRCA-2 mutation has a life time risk of ovarian cancer 13-23% | Offer risk reducing surgery (BSO) after the age of 35 years when child bearing is complete. May be delayed until the age of 45 years because of later age of onset but may lose the benefit of reduction in breast cancer risk |
| HNPCC or Lynch syndrome has life time risk of ovarian cancer 3-14% | Offer risk reducing surgery (BSO) with concomitant hysterectomy after child bearing is complete because of the risk of developing ovarian and endometrial cancer. |

Role of salpingectomy

The site of origin of pelvic (ovarian, fallopian tube, peritoneal) high grade serous carcinoma has been the subject of debate. One of the theories proposed involved malignant transformation of distal fallopian tube mucosa through P-53 signatory and the development of serous tubal intra epithelial carcinoma (STIC). These STIC lesions may invade locally into the underlying tubal wall, exfoliate on to the surface of the ovary or peritoneal

cavity or a combination of these. This exfoliation into the peritoneal cavity could explain the clinical finding of widespread high grade serous ovarian carcinoma in the absence of significant volume of invasive disease in the fallopian tube and ovary.²⁶

In high risk women with an identified BRCA mutation, BSO offers the greatest risk reduction of ovarian cancer and significant reduction of breast cancer. Bilateral salpingectomy with delayed oophorectomy may be a cost effective strategy that could overcome the quality of life issues associated with bilateral oophorectomy in premenopausal women.²⁵

A 2014 RCOG scientific impact factor opines that women who are not at a high risk of BRCA mutation and have completed their families should be carefully considered for prophylactic removal of fallopian tubes with conservation of ovaries at the time of gynaecological or other intraperitoneal surgery.²⁷

Other protective factors

Include multiparity, breast feeding, tubal ligation, hysterectomy and oral contraceptive pills (OCP) usage. OCP use is associated with decreased risk of ovarian cancer and protective effect persists for a longer time after stopping its use.

CONCLUSION

Majority of epithelial ovarian cancers are detected in late stages with poor survival rates. Based on various trials at present there is no role for screening asymptomatic average risk women. High risk women require multi-modality screening and risk reducing surgery. Results of UKTOCS are awaited which is the largest trial, though initial results showed increased detection of early ovarian cancer. Further research is also needed in biomarkers.

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