Editorial

Screening for Ovarian Cancer: An Update

I, the ovary, possess a mysterious physiology
that affects all organs from head to toe,
It is for the vigilant clinicians to decide
they want me as a friend or a foe!

The ovaries are the most mysterious and the least accessible of the female reproductive organs. The mystery lies in their intricate functional relationship with many organs and systems in the body leading to a myriad of maladies arising from and developing in their multiple constitutional tissues/structures. The relative inaccessibility of the ovaries often leads to a delay in detection of ovarian disorders including borderline tumors and ovarian malignancies.

Worldwide, the number of new cases of ovarian cancer each year is approaching 250,000.[1] Although the risk of developing and dying from ovarian cancer is almost twice as high in developed countries when compared to less developed countries, the actual burden is much higher in less developed countries due to population sizes (World Ovarian Cancer Coalition Atlas, April 2018). As per the Population-Based Cancer Registry in India, Ovarian cancer is one of the five leading sites of cancer. The age-standardized incidence rate of ovarian cancer increased substantially by 28.6% from 1990 to 2016 (Lancet Oncology, September 2018).

Factors which predispose to ovarian cancer include infertility (based on the incessant ovulation theory and the gonadotropin theory), family history/genetic factors (BRCA1, BRCA2 gene mutations or MSH2, MLH1, PMS1, and PMS2 gene mutations in Lynch II syndrome) and previous hormone therapy. A study on Danish women aged 50–79 years over a period of 10 years concluded that risk for Ovarian cancer is increased with hormone therapy, regardless of duration of use, formulation, estrogen dose regimen, progestin type, and administration route.[2] However, I am of the opinion that the translated risk was very small in this study (one extra ovarian cancer for approximately 8300 women taking HT each year) and more multicentric trials are required. The use of talcum powder on the vulva and perineum[3] and high lactose consumption has been associated with increased risk of ovarian cancer.[4] Women who are at a higher risk for ovarian malignancy by virtue of their family history or genetic predisposition need to be aware of it. They should be extra cautious and aim to detect ovarian malignancy at the earliest stage should it occur.

Epithelial ovarian cancer is the most common form of this disease with a 46% overall 5-year survival rate

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by FIGO staging. Mortality rates from ovarian cancer vary by stage at diagnosis; 5-year survival rates range from 92.5% for localized cancer to 28.9% for cancer with distant spread.[5] Even though ovarian cancer is less common as compared to other gynecological malignancies like cervix, mortality due to this is quite high due to late detection. Mortality rates can be improved through prevention, screening, early detection, and optimal management.

In general, a good screening test should be inexpensive, should be easy to administer, should cause minimal discomfort, should be consistently reliable and should be valid. The validity of the test is its ability to accurately distinguish between diseased and nondiseased individuals. Therefore, it should be highly sensitive as well as highly specific. Besides this, the screening program should be designed for the population section which has the highest prevalence of the disease to ascertain a satisfactory positive predictive value. Finally, the screening test should definitely show improvement in morbidity and mortality in that particular population section.

The search for an ideal screening test for ovarian cancer has been going on for quite some time now. Transvaginal ultrasound, CA-125, and bimanual pelvic examination have been used in various screening studies to evaluate their role as screening tests but have not found much supportive evidence. Recently, the United States Preventive Services Task Force (USPSTF) reviewed the evidence on benefits and harms of screening for ovarian cancer in asymptomatic women not known to be at high risk for ovarian cancer. The USPSTF found that screening for ovarian cancer conferred no mortality benefit and that harms in the form of false-positive screening test results and subsequent surgery were moderate to substantial. Therefore, the USPSTF recommended against screening for ovarian cancer in asymptomatic women (level D) who are not at high risk for the disease.[6]

Among the three good quality studies identified by USPSTF, the largest and the most recent was

the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS). The UKCTOCS was a randomized clinical trial of 202638 postmenopausal women aged 50–74 years not known to be at high risk of ovarian cancer.[7] In this trial, women were randomized to screening with serum CA-125 testing, with triage and follow-up determined by ROCA (multimodal screening), or to yearly Transvaginal sonography (TVS). After a median follow-up of 11.1 years, there was no significant difference in mortality due to ovarian cancer (including mortality from primary peritoneal and fallopian tube cancer) among the control group and the two intervention groups (0.35% in the control group, 0.32% in the TVS group, and 0.32% in the CA-125 ROCA group).[8] The much smaller pilot study for UKCTOCS, UK Pilot evaluated the use of a single cutoff value for CA-125 testing and found no significant difference in ovarian cancer mortality (excluding primary peritoneal cancer) between women who were screened and those who were not screened (0.08% vs. 0.16%; relative risk, 0.50 [95% confidence interval [CI], 0.22–1.11]).[8,9]

In the prostate, lung, colorectal, and ovarian cancer (PLCO) trial conducted in the US, no difference was found in the ovarian cancer mortality (including primary peritoneal cancer) with 0.34% in the screening group and 0.29% in the usual care group (RR 1.18 [95% CI, 0.82–1.71]).[8,10] In this trial, 68,557 women aged 55–74 years who had at least one ovary at baseline were randomized to either annual screening (both CA-125 and TVS for first four rounds of screening, then two rounds of CA-125 testing only) or usual care after ruling out previous diagnosis of lung, colorectal, or ovarian cancer. Median follow-up was for 12.4 years.

Surgery to investigate positive screening test results among women who ultimately did not have ovarian cancer occurred in 0.2% of participants in the UK Pilot CA-125 group, 0.97% of participants in the UKCTOCS CA-125 ROCA group, 3.25% of participants in the UKCTOCS ultrasound group, and 3.17% of participants in the PLCO CA-125 plus ultrasound group.[8] Up to 15% of these women had major surgical complications.[8]

The USPSTF identified limited evidence on the psychological harms of screening for ovarian cancer from the UKCTOCS and QUEST trials.[8,11,12]

The American Cancer Society and the American College of Obstetrician and Gynecologists (ACOG) also do not recommend screening for ovarian cancer in average-risk women. However, the ACOG does recommend that the evaluation of high-risk women may include transvaginal ultrasound and CA-125 testing in addition to the physical examination.

Memorial Sloan Kettering (MSK) in its screening guidelines recommends that women with increased risk for ovarian cancer due to reasons other than genetic mutations may be offered screening within the framework of research studies to evaluate the efficacy of this approach after thorough counseling. For women with genetic mutations, ovarian cancer screening using a combination of CA-125 and TVS should be done. MSK begins screening women with mutations in BRCA1 or the mismatch repair genes MLH1, MSH2, and MSH6 between 30 and 35 years of age. For women with BRCA2 mutations, screening is initiated between 35 and 40 years of age. The National Comprehensive Cancer Network (NCCN) recommends risk-reducing salpingo-oophorectomy (RRSO) in women with BRCA1/2 mutations after 35 years of age. In women not undergoing RRSO, transvaginal ultrasound combined with serum CA-125 may be considered at the clinician's discretion starting at the age of 30–35 years (NCCN Guidelines Version 3.2019).

Currently, ovarian cancers are classified as Type I or low-grade cancers and the more common Type II or high grade/aggressive cancers. There are specific molecular markers for each type of cancer. Alterations of K-ras/B-raf pathways in fimbrial cells are thought to lead to low-grade cancers and p53 mutations to high-grade cancers.[13] Finding early low-grade cancers by presently available screening tools or early detection means will have no impact on the survival of high-grade cancers which carry a poorer prognosis.[14] Basu *et al*. studied the status of transforming growth factor beta (TGF-β) signaling in human ovarian tissues by immunohistochemistry. They found that invasion-associated genes SNAI1 and MMP9 acted as important mediators of pituitary homeobox 2 (PITX2)-induced invasiveness of ovarian cancer cells through TGF-β pathway. PITX2 overexpression resulted in the loss of epithelial markers and gain of mesenchymal markers that contributed significantly to ovarian oncogenesis.[15] Genetic expression based on molecular profiling will have significant implication in screening, early detection, and customized targeted treatment strategies for ovarian cancer in the future.

With ample research going on in this field, we hope to see effective screening modalities for ovarian cancer which will contribute significantly to reduce mortality due to this dreaded disease!

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Access this article online	
Quick Response Code:	Website: www.jmidlifehealth.org
	DOI: 10.4103/jmh.JMH_46_19

How to cite this article: Patni R. Screening for ovarian cancer: An update. J Mid-life Health 2019;10:3-5.