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THE ROLE OF IMAGING IN SCREENING SPECIAL FEATURE: REVIEW ARTICLE

Ovarian cancer screening—ultrasound; impact on ovarian cancer mortality

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ABSTRACT

Although ovarian cancer (OC) is the most lethal of all female malignancies, debate still exists concerning the benefits and harms of the screening programs and their impact on long-term survival and mortality from the disease. The most widely tested screening strategies have focused on transvaginal ultrasound (TVU) and on algorithms that measure serum levels or interval changes of cancer antigen–125 (CA-125) either individually or in combination. Transvaginal ultrasound can identify size and morphology changes of the ovary that may signal a developing malignancy; yet, it is still accused of having a low specificity. There is preliminary evidence that screening can improve survival, but the impact of screening on mortality from OC is still unclear and warrants further validation. In spite of having many published prospective studies, up to-date, none have been able to demonstrate conclusively a reduction in mortality from OC both in the screened general or high-risk population. Data from the US Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial has not shown survival or mortality benefits in the general population. Most prospective trials have reported a decrease in stage at detection (with the exception of the PLCO trial), thereby allowing treatment to be initiated when the disease is most curable. Research is in progress to develop new diagnostic tests and novel biomarkers, which when used in combination can increase the accuracy and outcomes of screening. In this review article, we will discuss the debate provoked on OC screening programs and the impact of using ultrasound on the reduction of OC-related mortality.

INTRODUCTION

Population-based screening programs for cancer aim to increase the life expectancy of cancer patients and to reduce mortality rates by identifying cancer at earlier and more curable stages. Cancers which benefit from adopting screening programs should be common in the population with a well-understood natural history. There should be an easy and reliable test that can detect cancer at an early and potentially curable stage while maintaining the balance between the benefits of early detection against the cost of screening. In addition, there should be an acceptable treatment option that is more effective if started early in the disease process.[1,2]

Worldwide, many countries have adopted screening programs for the early detection of breast and cervical cancer in the female general population, yet, there is no similar validated screening strategy for ovarian cancer (OC). OC is asymptomatic and is usually diagnosed at late stages; thus, it is considered the most lethal of all female malignancies. Although fulfilling many criteria for screening legibility, debate still exists concerning the benefits and harms of developing screening programs for OC.[3]

In this review article, we will discuss the debate provoked on the screening programs of the OC and the impact of using ultrasound—as a screening imaging modality—on the reduction of mortality.

Incidence and prognosis ovarian cancer

OC is the fifth most common cancer in females. It is diagnosed annually in nearly 250,000 females globally, and is responsible for 140,000 deaths each year. Statistics show that OC carries a very poor prognosis with the lowest survival rate of all gynecological malignancies. One of the reasons for the high mortality rate of OC is that early stage symptoms are few and non-specific.[3–7]Only 20–25% of OC patients are diagnosed with Stage I disease in which

the 5-year survival rates are greater than 90% while 75–80% are diagnosed with Stage III or IV in which the 5-year survival rates range from 17 to 39%.[8]

The opportunity to improve outcomes and prognosis of OC is through both early detection and risk stratification methods.[9]

Risk stratification and the value of adopting personalized ovarian cancer screening programs

The risk of developing OC increases with age and the median age at presentation is 60–63 years. The strongest genetic risk factors for developing OC are *BRCA1* and *BRCA2* genetic mutations. The estimated lifetime risk of developing OC may be as high as 46% in females who are *BRCA1*-positive, and 17% in females who are *BRCA2*-positive.[10]Females with Lynch syndrome (hereditary non-polyposis colon cancer), or those who have a family history of OC are also considered at increased risk. The "increased-risk family history" generally means having two or more first- or second-degree relatives with a history of OC or a combination of breast and OC.

Other factors which may be associated with a reduced risk of OC include the use of oral contraceptives, pregnancy, breastfeeding, bilateral tubal ligation, and the removal of the ovaries.[11]

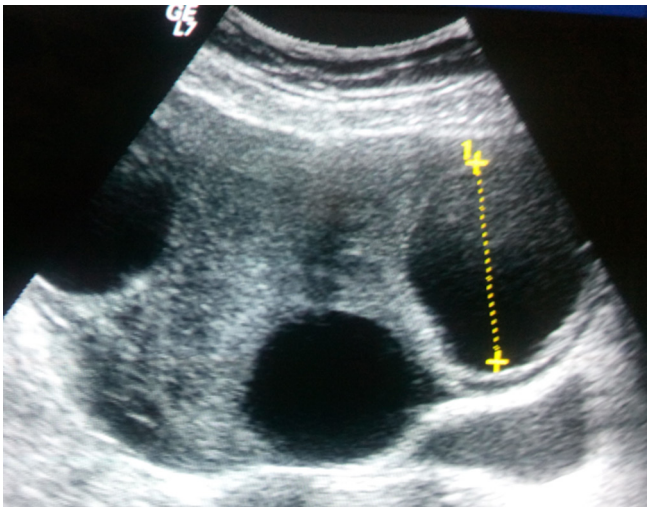
The prospect of OC personalized screening according to genetic risk stratification has become feasible given the advances in genetic technology.[9]Currently, population-based OC screening is not recommended for asymptomatic females at average risk of the disease as intense research have failed to produce a clinically effective and applicable screening strategy.[12–14]

At present, efforts are under way to provide and authenticate risk-prediction models for OC that incorporate risk stratification based on personal and family history together with early detection and diagnosis (PROMISE 2016 "Predicting Risk of Ovarian Malignancies, Improved Screening and Early Detection ").[15] The benefit of risk-stratified screening incorporating genotyping is that individuals could be offered customized interventions and in the same time maintaining early cancer detection rates. The algorithm and frequency of screening can be also specifically designed based on the OC-risk profile. Females with a greatly increased risk for developing OC may benefit from risk-reducing surgery or chemoprevention. Individuals at lowest risk might waive screening, whilst those at highest risk might start screening at earlier ages. Applying this, the harms associated with screening specifically over diagnosis and unnecessary treatment can be alleviated.[16] Focusing screening on females at the highest genetic risk would also make screening possible and cost-effective.[17]

Current tools for ovarian cancer screening

The most widely tested screening strategies have focused on transvaginal ultrasound (TVU) and on algorithms that measure serum levels or interval changes of cancer antigen-125 (CA-125) either individually or in combination.[18–21]

Figure 1. False-positive high CA-125 level in a 28-year-old female with over simulated ovaries secondary to hormone intake. Ultrasound showed increased ovarian volume, hypertrophied ovarian stoma and multiple large cystic spaces, *i.e.* follicles. The ovary regained its normal size and morphology on follow-up ultrasound examinations. CA-125, cancerantigen-125.



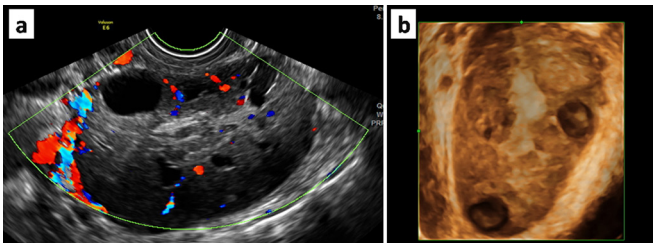
Cancer antigen-125 (CA-125) and novel serum biomarkers

CA-125 is a high molecular weight glycoprotein that is noted in the blood stream in the presence of epithelial ovarian tumors. It shows high values in about 50% of early stages (Stage I) of OC and up to 90% of the patients with advanced disease.[22] Each female has her own CA-125 baseline and significant increases above this level may identify cancers earlier. Measuring CA-125 serum level is not accurate, and many false-positive results have been previously recorded in benign diseases[23] (Figure 1). To reduce false results, an algorithm was followed in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).[3] In the UKCTOCS, the risk of ovarian cancer calculation assessment (ROCA) is followed by plotting interval changes of serum CA-125 concentration. This helps in identifying significant rises in CA-125 concentration above baseline (30 U ml^{-1} or greater).[3] Using ROCA, females's risk of developing OC can be classified into three levels: *low risk* (need annual screening), *intermediate* (need a repeat of CA-125 titre after 12 weeks), and *elevated* (requires a repeated CA-125 concentration and TVU as an adjunct test in 6 weeks).[3,24–27] Females with persistent abnormalities are referred to surgery.

In another attempt, a number of novel biomarkers that are both sensitive and specific for early-stage disease are being investigated given the latest progresses in genomic and proteomic research. Although up till now CA-125 has been the focus of most investigations, other biomarkers elicit promising results as human epididymis protein (HE4), the OVA1 panel, and the Risk of Malignancy Algorithm.[18,28]

Integrating imaging techniques with specific novel serum biomarkers assessment may have the potential to provide an effective screening strategy.[18,29–33]

Figure 2. (a, b) A patient complaining of dysfunctional uterine bleeding showed benign looking ovarian mass that was surgically excised and proved to be fibrothecoma. The ovarian volume was increased and a solid mass lesion was seen replacing the ovarian stroma evident in the 2D Doppler (a) and the 3D TVU (b). 2D, two-dimensional; 3D, three-dimensional; TVU, trans vaginal ultrasound.



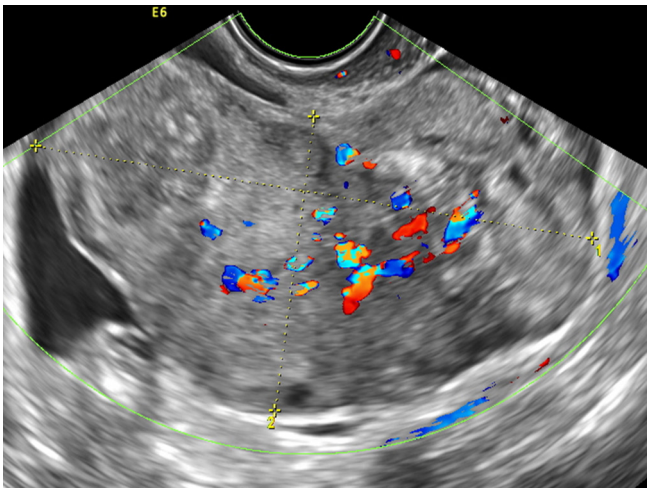
Transvaginal ultrasound screening

In the last three decades, the potential efficacy, acceptability and draw backs of ultrasound both individually or as part of a multimodal approach to OC screening have been assessed in several studies.[34–36] TVU has been first considered as a promising imaging tool for OC screening due to its ability to measure volume and detect morphology changes of the ovary that may signal a developing malignancy.[37]

For screening to be effective, there should be standardized evaluation of screen-detected ovarian abnormalities. Criteria for ovarian abnormality on TVU vary from one screening model to another, but they usually include both volume and morphology. Morphology abnormality is based on the presence of solid areas or papillary projections from the cyst wall in a complex cystic ovarian tumor or a solid ovarian tumor with an abnormally increased volume.[36–38]

The low specificity of ultrasound-screening due to the overlap between benign and malignant masses poses a challenge (Figures 2 and 3).To minimize false-positive results, a repeated ultrasound examination is recommended in some studies to confirm the nature of the screening identified ovarian mass

Figure 3. Ovarian torsion: TVU displayed marked increase of the ovarian volume that showed multiple suspicious irregular vascular that was misdiagnosed as malignant mass. In the follow-up study; CA-125 was normal and the ovary regained normal volume and morphology. CA-125, cancer antigen-125; TVU, trans vaginal ultrasound.



(Figure 4).[39,40] Other screening protocols generated scoring scales relating ovarian tumor morphology to risk of malignancy.[41,42]

RATIONALE OF OVARIAN CANCER SCREENING AND IMPACT ON MORTALITY

A close correlation exists between the stage of OC at presentation and survival; therefore, early detection of OC has always represented the best hope for mortality reduction and long-term survival. There is preliminary evidence that screening can improve survival, but the impact of screening on mortality from OC is still unclear and warrants further validation. In spite of having many published prospective studies that is concerned with that issue, yet, up to-date none have been able to demonstrate conclusively a reduction in the mortality from OC in the general or high-risk screened populations.[41,43,44] Based on this, The United States Preventive Services Task Force recommends

Figure 4. Cystic ovarian mass. (a) Color Doppler, and (b) grayscale ultrasound images. The mass is complex cystic in (a, b) that showed multilocularity and turbid slightly echogenic mesh like content. The complex cyst evolved over time (after 2 weeks follow-up for one and half month duration). The cyst in (c) showed simple characteristics and become unilocular of clear content and thin unifrom walls.

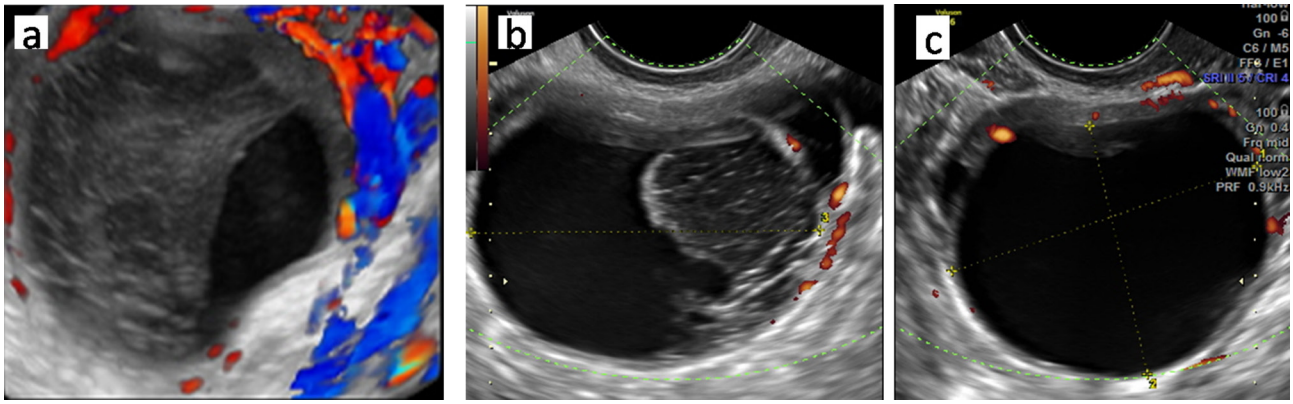
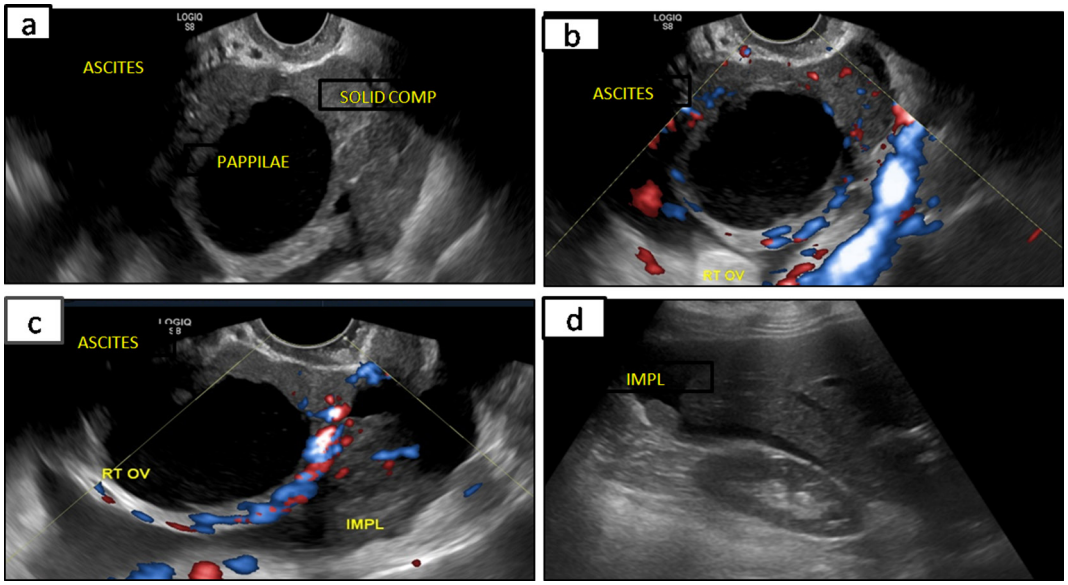


Figure 5. A 40-year-old female with a right adnexal small complex malignant mass lesion (a, b). There was an association of extensive ascites and multiple peritoneal implants (c, d).



against screening for OC in asymptomatic females, except in those with known genetic mutations that increase the risk for OC.[45,46]

Assessing the effectiveness of OC, screening programs and their impact on mortality is extremely challenging. Despite the high mortality rates from OC, the disease occurs infrequently which means that the impact of any screening test on mortality can be only achieved by very large prospective randomized trials over long periods of time.[47,48] Many of those who are diagnosed with OC in screening programs turn out to be false-positive cases which eventually affected the renowned prevalence of the disease.[47] A positive predictive value of only 10% requires at least a specificity of 99% and a sensitivity of more 75% of the screening test, even if the selected cases are those above 50 years of age who have an increased risk of OC.[48] There is also no *in-situ* stage of OC that can be identified on imaging and most cases present with advanced disease.[47–49] It was even believed that some OCs might be of aggressive phenotypes with a poor prognosis even when discovered early[18] (Figure 5).

Thus, there has been great concern as regards the capability to develop an effective screening strategy that has the potential to improve mortality from OC.

Ovarian screening trials in the general population

Several large-scale clinical trials have used primary ultrasound screening or multimodal strategies incorporating ultrasound to evaluate the detection of OC. The two largest screening trials that reported OC incidence and mortality for females randomized to OC screening vs no screening were the PLCO (Prostate, Lung, Colorectal and Ovarian randomized trial)[50–54] and the UKCTOCS (UK Collaborative Trial of Ovarian Cancer Screening).[3] Both trials tested annual screening of the general population by assessing CA-125 serum level and/ or TVU, yet, unfortunately, these two trials show conflicting preliminary findings (Table 1).

The UKCTOCS trial is the first randomized controlled trial of OC screening to produce somewhat relatively promising results as regards screening postmenopausal females from the general population. The UKCTOCS trial began enrolling participants in 2001. The trial was preceded by a smaller trial (n = 21,935) that was conducted by the same research group (UK. Pilot).[51–55] Over 200,000 (n = 202,546) post-menopausal females were enrolled from 13 NHS centers in England, Northern Ireland and Wales. The UKCTOCS had two intervention arms and a no-screening, control arm (1:1:2 respectively). Participants were randomly assigned to undergo annual multimodal screening (MMS) by serum CA125 levels interpreted using the ROCA, TVU, or no screening. The median follow-up was 11 years, and more than 1200 OCs were diagnosed. A positive screen was defined as a positive initial screen that eventually led to surgery. A statistically significant earlier stage of OC was reported in screening arms compared with control arms ($p < 0.005$). Analysis of the results showed that reduction of OC mortality by 15% with MMS and 11% with TVU, compared with no screening. These results are comparable to that achieved by breast cancer screening (15–25%). It was estimated that 641 females would need to undergo MMS in order to prevent one death from OC.[3]Although initial outcomes of MMS in the UK trial appeared encouraging, yet there was no significant impact on mortality rates when ultrasound was used as the primary modality. Furthermore, OC mortality was not significantly different among the control group and 2 intervention groups (0.35% in the control group, 0.32% in the TVS group, and 0.32% in the CA-125 ROCA group). There was also no significant difference in mortality risk in the TVU and CA-125 ROCA groups. Longer follow-up is still needed to verify the results and assess the potential of a delayed mortality benefit for screening the general population and whether it would be cost effective or not.[3]

The PLCO trial is the only US-based study that assesses the possible net benefits or harms of screening. In the OC portion of the PLCO trial, investigators at 10 US centers randomized 78,216 females either to annual screening for OC or to usual care. Females in the intervention arm of PLCO underwent a maximum of six rounds of screening (four with CA-125 and ultrasound, two with CA-125 alone). Participants were followed for a median of 12.4 years for cancer diagnosis and mortality. When the trial ended, OC had been diagnosed in 212 females in the screening group and 176 females in the usual care group with a calculated relative risk of 1.2. A positive screen was defined based on the results of the initial screening tests. About 80% of the diagnoses in both groups were advanced disease: Stage III or Stage IV which means that screening did not change the expected stage distribution between both arms. As regards mortality, 118 females in the screening arm died of OC compared with 100 in the control group with a calculated mortality relative risk of 1.18 for the screened females. Buys and co-authors noted that the PPV was 3.7% for an abnormal CA-125 test, 1.0% for an abnormal TVU, and 23.5% if both tests were abnormal. In the screening arm, about 3285 participants (5%) of participants had false-positive results, of whom 1080 underwent surgical interference. Although these figures are still comparable to mammography screening results, yet the follow-up protocol which often entailed invasive procedures were considered of serious concern. Buys and co-authors concluded that dual screening for OC failed to reduce female's risk of death from the disease.[50] In a recent updated review of the PLCO, Pinsky and co-authors confirmed that there was no decrease in mortality in the intervention group when compared to the control group. They also reported potential harms of screening.[52]

Another multicenter OC screening prospective randomized trial in asymptomatic females was conducted in Japan between 1985 and 2002.[53] A total of 41,688 participants were assigned either to a screening arm (annual pelvis examination and TVU as a primary modality and serum CA-125 as a secondary one) or a control arm. Screenings were repeated yearly for an average of 5.4 screens and a mean follow-up of 9.2 years. A total of 103 patients had ovarian lesions that showed high risk for OC out of which 64 underwent surgery. As in all the screening trials with the exception of the PLCO trial, regular ultrasound screening was associated with earlier disease stage in the screening arm were 63% had Stage 1 disease vs 38% in the control group, yet these results were not statistically significant (p: 0.23). The impact of the long-term screening on the OC mortality is not documented[53] [Table 1].

The University of Kentucky Ovarian Cancer Screening Trial started since 1987, and had enrolled 41,413 females[54] [Table 1]. Eligibility criteria included all females 50 years and older and females 25 years and older if they have a documented family history of OC. This trial does not have a "no screening" control arm and the control population were females with OC outcomes reported in the Kentucky Tumor Registry. Females with abnormal TVU screens underwent tumor morphology indexing, serum biomarker analysis, and surgery. Data published from this trial reported that in the screening cohort 47% of cancers were detected at Stage I and 70% were detected with Stage I or II disease as compared to only 27% of those reported to the Kentucky Tumor Registry during the same time period ($p < 0.01$). The 5-year survival of screen detected OC was 74.8 ± 6.6% compared to 53.7 ± 2.3% for those reported to registry ($p < 0.001$). Fewer surgical complications were also reported.[54] The researchers concluded that, annual TVS screening of asymptomatic females achieved increased detection of early-stage OC cases and an increase in 5-year disease-specific survival rate for females with OC. Further analyses of these results have not been yet reported, and there are concerns as regards driving conclusions about the effectiveness of TVS screening based on a cohort comparison study design.[55]

Given the lack of mortality benefit of screening from OC screening trials in the general population, and the harms that could result from false-positive screening test results and consequent intervention, the United States Preventive Services Task Force has stated in the latest recommendation for OC screening that the harms of screening for OC with CA-125 testing, TVU, or both outweigh the benefits of screening since screening did not significantly reduce OC deaths.[45,46]

Ovarian cancer screening trials in the high-risk population

Research screening in high-risk population is mainly limited to prospective cohort study as random assignment to a non-screening arm in this group is both unacceptable and unethical.[56]

Lai and colleagues introduced another more recent analysis of the PLCO participants with a family history of breast or OC. They reported a non-significant difference in the diagnosis of Stage I or II cancers in the screened arm compared with the usual care arm (29 *vs* 17%; $p = 0.085$). They reported improved survival in screening detected OC; however, they confirmed this apparent improvement in survival still did not result in improving the OC mortality.[57]

The United Kingdom Familial Ovarian Cancer Study is the first published prospective multicentric cohort screening study in which 4,348 high-risk females were enrolled from 2007 to 2012.[58] The purpose of the study was to establish the performance of screening using the ROCA and TVU but this time for females with a lifetime risk ≥10% for developing OC. if ROCA results were normal, participants underwent ROCA screening every 4 months and TVU. Prophylactic salpingo-oophorectomy was encouraged during the study. The study is a non-randomized study with no non-screening arm and comparison was between screening identified cancers with OC diagnosed after screening ended. The median follow-up time was 4.8 years. 7 (36.8%) of the 19 cancers diagnosed less than 1 year after prior screen were Stage IIIb to IV as compared with 17 (94.4%) of 18 cancers diagnosed more than 1 year after screening ended. The authors concluded that ROCA-based MMS every 4 months is associated with significantly lower stage disease, and a significantly lower residual disease rate compared with females from the same cohort in whom cancer was diagnosed more than 1 year after screening ended. Although the authors concluded that ROCA-based screening—being highly sensitive—is an option

for females at high risk of OC, yet, it remains unknown whether this strategy would improve survival in the screened high-risk females or not and again no definite impact on mortality was reported.[58,59]

In 2017, Skates and co-authors combined data from prospective Cancer Genetics Network and Gynecologic Oncology Group trials in 3692 high-risk screened females. The researchers stated that females at high risk often undergo screening despite no proven validity. Serum CA-125 was evaluated using ROCA as each female has her own CA-125 baseline, and any significant increases above this baseline may signal the presence of OC rather than the standard reference of CA-125 more than 35 U ml^{-1} and thus, TVU would be indicated for further evaluation. Specificity and positive-predictive value were compared with levels calculated for the general population screening. They compared the "stage-at-detection" with that reported in past high-risk screening studies. They reported a specificity of 92% for TVU as compared to 90% for the general population (p = 0.0001), and positive-predictive value of 4.6% compared to 10% ($p > 0.10$). 50% of screening detected cancers were early stage as compared to only 10% in previous studies (p = 0.016). The authors concluded that for screened females at increased risk of developing OC, ROCA had better early-stage detection at high specificity, and low but satisfactory positive-predictive value compared with the standard CA-125 evaluation. At the end, the authors recommended further larger cohort studies to validate these results.[60]

BENEFITS AND HARMS OF USING TVS IN OC SCREENING

TVS was tested as a potential screening modality in many ovarian screening trials being safe and well -tolerated by patients. TVS has been included in most multimodal OC screening strategies to reduce false-positive results and to minimize falsies from measuring CA-125 serum levels. Measuring serum CA-125 levels has many false-positive and negative results and thus cannot be used a standalone screening modality.[61] In fact, most proposed screening strategies use biomarker driven strategies as the primary modality in combination with TVS. TVS was used as a primary screening modality in only two trials: the UKCTOCS TVS screening arm and Kentucky trials.[3,54] Although TVS is considered especially useful in distinguishing simple cysts from complex cystic masses and solid tumors, yet, we have to admit that TVS still has limited capability of identifying OC at its early stages and some ovarian tumors may even metastasize before reaching tumor volume sizes that can be detected by TVS. No TVS ovarian abnormalities were identified in some females included in studies assessing the role of TVS in high risk females despite many being in an advanced stage of disease.[62,63]The overlap in TVS features between benign lesions and early OC signifies another limitation of TVS. False-positive TVS results may also lead to the detection of disease that would not, eventually, cause mortality. False -positive results may also lead to unnecessary diagnostic intervention procedures to confirm or exclude OC mounting to removal of one or both ovaries with possible serious surgical complications.[45,46]

CONCLUSION

Knowing the natural history of OC, it is a real challenge how any screening strategy could identify OC at a more treatable stage that would have a delayed effect and impact on mortality from the disease. Ultrasound, although the imaging technique with the highest potential to be used for OC screening, is accused of being non-specific especially when there is no significant volume or morphology changes. For this reason, most of the widely tested screening strategies have focused on algorithms that incorporated TVU and serum level or interval changes of CA-125 assessment. However, despite numerous OC screening trials incorporating both techniques, there is still not yet conclusive evidence that OC screening reduces mortality and there is insufficient evidence to implement general population screening for OC at present. Although the encouraging results from the UKCTOCS trial has stimulated new efforts to refine the screening techniques, yet, future research on new biomarkers and new risk-assessment models is still essential and may give hope for finding an optimal combination of ultrasound with other screening tests.

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