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Review Article

Screening for ovarian cancer: Evidences

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ABSTRACT

Cancer of the ovary is a leading cause of death among women. Early stage disease are not evident for the incumbent nature of disease in the abdominal cavity. When ovarian cancer is detected and treated while it is still confined to the ovary (stage I), the 5-year survival rate is approximately 90%, but 33% when the disease is diagnosed at stage III or IV. So screening had role in down staging the disease and improve survival. Evidence still does not support screening in average risk women but annual gynecologic examination with pelvic examination is recommended for preventive healthcare. Screening in women with increased risk and inherited risk result in a decrease in the number of deaths in women. For women with mutations in BRCA2, ovarian cancer screening should be initiated between ages 35 and 40.

Keywords: Ovarian cancer, screening, ca 125, ultrasound

Incidence and Mortality

Ovarian cancer is the fifth leading cause of cancer death among women in the United States and has the highest mortality rate of all gynecologic cancers[1] It is estimated that 22,440 new cases of ovarian cancer will be diagnosed in the United States in 2017, and 14,080 women will die of this disease.[1] The median age at diagnosis is 63 years.[1] The prognosis for survival from ovarian cancer largely depends on the extent of disease at diagnosis, which is usually advanced, with only about 15% of women presenting with localized disease at diagnosis.[1,2] When ovarian cancer is detected and treated while it is still confined to the ovary (stage I), the 5-year survival rate is approximately 90%, but 33% when the disease is diagnosed at stage III or IV. [2] Lifetime risk of being diagnosed with ovarian cancer is 1.38%. [2] It looks like only the early detection can increase the survival of carcinoma ovary. In Nepal also, B.P. Koirala Memorial Cancer Hospital based data reflects carcinoma ovary being the 2nd most common gynaecological malignancy after carcinoma of cervix. Majority of disease also presents late in stage III or IV.[3] To detect this disease early, several methods of screening are opted. This review outlines the risks and options of screening available from the bench to the clinics.[4,5]

Ovarian Cancer Risk Types

1. Average Risk: Post-memopausal women age more than 55 years.
2. Women with risk level that of general population (RR < 3 times general population): nulli parity, menarche at an early age, menopause at a late age, fertility drug use and hormone replacement therapy use, are believed to put individuals at risk of disease. Age, Caucasian race, ethnicity (especially Ashkenazi Jewish heritage), living in an industrialized country, and a history of endometriosis are other factors predisposing to ovarian cancer.
3. Women with increased risk (RR >3-6 times of general population): first degree relative with ovarian cancer. Personal history of breast cancer prior to age of 40. A personal history of breast cancer diagnosed prior to age 50, and one or more close relatives diagnosed with breast or ovarian cancers at any age. Two or more close relatives diagnosed with breast cancer prior to age 50 or with ovarian cancer at any age.
4. Women with inherited risk (RR > 6 times the general population): BRCA1/BRCA2 mutation, MMR gene mutation like HNPCC.

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Evidence on screening in women at average risk:

In absence of significant risk factors, a woman at 55 years carries 1 in 72 life time risk of developing an ovarian cancer. Ovarian cancer often presents with persistent but vague symptoms, usually occurring after the cancer has metastasized. Some investigators have proposed the use of symptom indices as a method for screening for ovarian cancer. [6] Manual pelvic examination is a part of the routine pelvic examination.[7] The sensitivity and specificity of the pelvic examination are not characterized, but examination generally detects advanced disease. [8] There is no evidence for the benefit of this test for the early detection of and decreased mortality from ovarian cancer and it is not further considered. Other screening tests at the moment mainly include trans-vaginal ultrasound (TVS) and the serum cancer antigen 125 (CA-125) assay. These are often performed in combination.

There are few trials that has shown screening has detected early stages of disease which has also translated into survival benefit also. A pilot randomized control trial evaluated a multimodal screening approach with serial CA125 and pelvic ultrasound in a sample of almost 22,000 postmenopausal women.[9] Combined CA125 and ultrasound (US) screening was not only feasible but also preliminarily resulted in a survival advantage (median survival 72.9 months in the screened group vs. 41.8 months in the control group, p = 0.0112). Data from this trial have paved the way for larger randomized-control trials which aim to examine the impact of screening on mortality.

University of Kentucky ovarian cancer screening [10]

To estimate the effect of ultrasonographic screening on stage at detection and long-term disease-specific survival of women with epithelial ovarian cancer a screening was done for healthy women. Eligibility included all asymptomatic women aged 50 years and older and women aged 25 years and older with a documented family history of ovarian cancer. From 1987 to 2011, 37,293 women received annual ultrasonographic screening. Women with abnormal screen results underwent tumor morphology indexing, serum biomarker analysis, and surgery. Forty-seven invasive epithelial ovarian cancers and 15 epithelial ovarian tumors of low malignant potential were detected. No women with low malignant potential tumors experienced recurrent disease. Stage distribution for invasive epithelial cancers was: stage I, 22 (47%); stage II, 11 (23%); stage III, 14 (30%), and stage IV, 0 (0%). Follow-up varied from 2 months to 20.1 years (mean, 5.8 years). The 5-year survival rate for invasive epithelial ovarian cancers detected by screening was: stage I, 95%±4.8%; stage II, 77.1%±14.5%; and stage III, 76.2%±12.1%. The 5-year survival rate for all women with invasive epithelial ovarian cancer detected by screening as well as interval cancers was 74.8%±6.6% compared with 53.7%±2.3% for unscreened women with ovarian cancer from the same institution treated by the same surgical and chemotherapeutic protocols (P<.001). So the trial concluded annual ultrasonographic screening of asymptomatic women achieved increased detection of early-stage ovarian cancer cases and an increase in 5-year disease-specific survival rate for women with ovarian cancer.

The Shizuoka Cohort Study of Ovarian Cancer Screening (SCSOCS) [11]

SCSOCS trial was a prospective, randomized trial examining ovarian screening, via CA125 and US, in asymptomatic postmenopausal Japanese women between 1985 and 1999. Of more than 41,000 women who underwent screening, only 27 had detected ovarian cancer; at the prevalent screen, screening produced a detection rate of 0.31 per 1000. Ovarian cancer screening also identified a higher proportion of stage I cancers (63% vs. 38%, p=0.23) when compared to the control group. [11]

United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)[12,13]

The UKTOCS is a randomized, controlled trial of 202,638 postmenopausal women recruited in 13 trial centers across the United Kingdom during the period of 2001 to 2005. Women were randomly assigned to receive multimodality screening with CA-125 as a primary test and TVS as a secondary screen (multimodal group); an ultrasound only (ultrasound group); or no routine screening (control group). Women with abnormal results underwent further evaluation by a gynecologist and oophorectomy in cases in which such surgery was considered to be appropriate. In a preliminary report describing outcomes in the ultrasonography and multimodality groups in the first 4 years, surgery was performed in 845 of 48,230 women (1.8%) in the

ultrasonography group, 24 of whom were found to have invasive ovarian cancer; in comparison, surgery was performed in 97 of 50,078 women (0.2%) in the multimodality group, 34 of whom were found to have invasive ovarian cancer. Of 58 invasive cancers that were detected by screening in the two groups, 28 (48%) were stage I or II, with no significant difference. The sensitivity of the MMS and USS screening strategies is encouraging. Specificity was higher in the MMS than in the USS group, resulting in lower rates of repeat testing and surgery. This in part reflects the high prevalence of benign adnexal abnormalities and the more frequent detection of borderline tumours in the USS group. The prevalence screen has established that the screening strategies are feasible. It was noted encouraging evidence of a mortality reduction in years 7–14, but further follow-up is needed before firm conclusions can be reached on the efficacy and cost-effectiveness of ovarian cancer screening. [13]

The Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial [14]

Randomized controlled trial of 78216 women aged 55 to 74 years assigned to undergo either annual screening (n=39105) or usual care (n=39111) at 10 screening centers across the United States between November 1993 and July 2001. A positive finding was defined as a CA-125 level of more than 35 U per milliliter or trans-vaginal ultrasonographic evidence of an abnormal ovarian volume or an ovarian cyst with papillary projections or solid components. The intervention group was offered annual screening with CA-125 for 6 years and transvaginal ultrasound for 4 years. Participants and their health care practitioners received the screening test results and managed evaluation of abnormal results. The usual care group was not offered annual screening with CA-125 for 6 years or transvaginal ultrasound but received their usual medical care. Participants were followed up for a maximum of 13 years (median, 12.4 years [10.9-13.0 years]) for cancer diagnoses and death until February 8, 2010.

Main outcome measure was mortality from ovarian cancer, including primary peritoneal and fallopian tube cancers. Secondary outcomes included ovarian cancer incidence and complications associated with screening examinations and diagnostic procedures.
Ovarian cancer was diagnosed in 212 women (5.7 per 10,000 person-years) in the intervention group and 176 (4.7 per 10,000 person-years) in the usual care group. There were 118 deaths caused by ovarian cancer (3.1 per 10,000 person-years) in the intervention group and 100 deaths (2.6 per 10,000 person-years) in the usual care group (mortality RR, 1.18; 95% CI, 0.82-1.71). Of 3285 women with false-positive results, 1080 underwent surgical follow-up; of whom, 163 women experienced at least 1 serious complication (15%). There were 2924 deaths due to other causes (excluding ovarian, colorectal, and lung cancer) (76.6 per 10,000 person-years) in the intervention group and 2914 deaths (76.2 per 10,000 person-years) in the usual care group (RR, 1.01; 95% CI, 0.96-1.06). Conclusions drawn from the study is among women in the general US population, simultaneous screening with CA-125 and transvaginal ultrasound compared with usual care did not reduce ovarian cancer mortality. Diagnostic evaluation following a false-positive screening test result was associated with complications.

Evidences in screening for High risk population:

Current opinion suggests that screening may be appropriate for women in these increased risk categories. However, while intensive screening is recommended for women with BRCA1 and 2 mutations, studies have indicated that screening with CA125 and TVUS are ineffective because the majority of cancers are still detected at advanced stages.[15] In a retrospective study of 241 women with confirmed BRCA1 or BRCA2 mutations, surveillance with annual pelvic exam, transvaginal ultrasound and serum CA125 level failed to effectively identify women with early stage disease.

Auranen and colleagues performed a systematic review of the literature to determine the role of screening in women with HNPCC or with a family history of HNPCC.[16] Of five studies meeting inclusion criteria, only three examined the utility of CA125 surveillance for ovarian cancer in this patient population. In total, five ovarian cancer cases, none of which were reported as early stage disease, were detected by CA125 surveillance. Based on the current available published evidence, the authors concluded that there is no benefit for ovarian cancer screening in this patient population. In summary, while studies have failed to demonstrate a benefit for screening in high risk patients, risk-reducing surgery is the most cost-effective gynaecologic cancer prevention

strategy and screening with serial CA125 levels and TVUS is generally recommended until risk-reducing surgery can be performed.[17]

HARMS FROM SCREENING

The PLCO trial provides the most reliable data to date on screening-related harms.[14] The rate of minor complications associated with CA-125 and TVS, such as bruising or fainting, occurred at a rate of 58.3 cases per 10,000 women screened with CA-125 and 3.3 cases per 10,000 women screened with TVS. Major complications associated with the diagnostic procedures among women diagnosed with ovarian cancer included infections, blood loss, bowel injury, and cardiovascular events. At least one major complication was reported among 52% of women diagnosed in the usual-care group and 45% among women diagnosed with ovarian cancer in the screened group.

False-positive tests occurred among 3,285 women, translating to a rate of about 5% at each screening round. The majority of false-positive tests (60%) result from TVS. Of the 3,285 women with false positive results, 33% underwent surgery. Of the 1,080 women who underwent surgery, 15% had 222 major complications, for a rate of 20.6 complications per 100 surgical procedures.[13] Women in the intervention group were more likely to have had an oophorectomy than those in the control group. Rates of oophorectomy were 85.7 per 10,000 person-years in the screened group compared with 64.2 per 10,000 person-years in the usual-care group (rate ratio, 1.33; 95% CI, 1.24–1.43).[13]

TOOLS OF SCREENING:

1. Trans-vaginal Ultrasound

TVS has been proposed as a screening method for ovarian cancer because of its ability to reliably measure ovarian size and detect small masses.[10]TVS as an independent screening modality is being evaluated in one arm of the United Kingdom Collaborative Trial of Ovarian Cancer Screening (UKCTOCS).[12]

2. Serum Markers:

2.1. CA125: CA-125 is a tumor-associated antigen that is used clinically to monitor patients with epithelial ovarian carcinomas.[16,17] Measurement of CA-125 concentrations has been proposed as a potential marker for the early detection of ovarian cancer, either as a single test with a threshold cut point or in algorithms examining the change in levels over time. The most commonly reported CA-125 reference value that designates a positive screening test is 35 U/mL. In one prospective screening study, the specificity of CA-125 levels of 35 U/mL was 97.6%.[13]

CA-125 velocity has also been examined using a multiple logistic regression model within the PLCO trial as a predictor for the development of ovarian cancer.[17] Both CA-125 velocity and time intervals between screening tests were associated with the development of ovarian cancer. The risk of ovarian cancer increased as velocity (measured as U/mL per month) increased, and the risk of ovarian cancer decreased when the time intervals between screening tests increased.

2.2. Other Potential Marker panels:

Research continues to find other biomarkers that either alone or in combination with CA-125 concentrations may lead to the early detection of ovarian cancer. A panel of biomarkers that included CA-125, HE4, transthyretin, CA15.3, and CA72.4 was evaluated using specimens assembled from multiple cohort and randomized trials, including the PLCO trial.[18] The phase II and III biomarker studies concluded that CA-125 remained the "single-best biomarker" for ovarian cancer. Another retrospective study, nested within the PLCO trial and included 118 ovarian cancer cases and 8 controls per case, evaluated 7 proteomic biomarkers (apolipoprotein A1, truncated transthyretin, transferrin, hepcidin, beta-2 microglobulin, connective tissue activating protein III, and inter-alpha-trypsin inhibitor heavy-chain) in addition to CA-125.[19] The addition of the seven protein biomarkers to CA- 125 did not improve the sensitivity beyond the use of CA-125 levels alone. This contrasted with this same group's preliminary evaluation of these markers using post-diagnostic rather than pre-diagnostic blood samples.[20]

2.3. Ciphergen Panel: Apoliporotein A1 and transthyretin (both down-regulated), and a fragment of inter-α-trypsin (up-regulated) in ovarian cancer. The three markers plus CA 125 had a sensitivity of 74% for early stage disease and specificity of 97%. [20]

2.4. Yale's Panel : antibody microarrays to identify four proteins that distinguished ovarian cancer: leptin, prolactin, osteopontin, and insulin-like growth factor II. The combination had a sensitivity of 95% and specificity of 95% for distinguishing ovarian cancer in all stages.

2.5. Luminex Panel: Lokshin et al., from the Univ. of Pittsburgh used the "bead-based" Luminex system for multiplexing many antibody-based assays to distinguish ovarian cancer cases from controls. Eight biomarkers had the highest diagnostic power including: CA 125, CA 19-9, EGFR, G-CSF, Eotaxin, IL-2r, cVCAM, and MIF. For postmenopausal ovarian cancer the sensitivity was 100% at a specificity of 98.6%. [21]

Joint efforts are being made to identify the current "best" panel of ovarian cancer markers in a "pre-validation" set of case-control specimens and then apply that panel to the pre-diagnostic specimens from the PLCO screening trial.

3. Risk of ovarian cancer algorithm (ROCA)[22]

Statistical analyses of serial CA125 levels showed each woman has her own baseline level, and in ovarian cancer cases, CA125 rose rapidly from her baseline following a change-point. Improved early detection of ovarian cancer may result if each woman were tested for the presence of a change-point CA125 profile. Using the serial CA125 from the completed trials, a statistical method was developed to measure the probability a change-point had occurred. For women with ovarian cancer however, the CA125 profile showed rapidly increasing levels above each woman's baseline prior to diagnosis. An increase in screen sensitivity might be obtained through utilizing this contrast in CA125 profile while maintaining the very high specificity previously established. A woman with a low baseline followed by a change-point where CA125 levels increase significantly above the baseline, may be detected earlier than when a fixed reference level of 35U/mL is applied.

Having developed the machinery for calculating a risk of having a change-point based on a woman's age and CA125 profile, the calculation is implemented in a screening program by prescribing decisions for each level of risk.[22] The implementation defines a screening algorithm, termed the risk of ovarian cancer algorithm (ROCA). Within ROCA, intermediate and elevated levels of risk are defined, the first indicating a low level screening intervention, and the second a high level intervention. In trials of women at normal risk where CA125 is tested annually, an intermediate ROCA risk triggers a CA125 test in three months and the risk is recalculated. Elevated ROCA risk triggers referral to a trans-vaginal scan (TVS). In women at high risk due to a multiple family history of ovarian or breast cancers, an intermediate ROCA risk triggers referral to TVS, while an elevated ROCA risk results in a referral for TVS and a consult from a gynecological oncologist.

This ROCA is being evaluated in the UKCTOCS. The UKCTOCS is evaluating two-stage screening with ROCA as the primary screen and TVS as a secondary screen (based on results of the ROCA) for its impact on ovarian cancer mortality compared with TVS alone or no screening. Estimated sensitivity data for multimodality two-stage screening with ROCA followed by TVS has been published from the prevalent screen. Of the 50,078 women who underwent the prevalent screen in the multimodality screening arm, 409 were determined to have an intermediate or elevated risk of ovarian cancer based on the ROCA and were referred for TVS. Of the 409 women, 167 women were referred for clinical evaluation, 97 underwent surgery, and 42 were diagnosed with either malignant ovarian or fallopian tube cancers. Among the women who had negative screens, five were diagnosed with ovarian or fallopian tube cancer within 1 year of screening. The estimated sensitivity was 89.4% (95% CI, 76.9–96.5%).[12]

CONCLUSION OF RECOMMENDATIONS AT PRESENT LEVEL OF EVIDENCES:

1. Women with a risk near that of the general population (relative risk less than three times greater than that of the general public) Ovarian cancer screening is not recommended. An annual gynecologic examination with pelvic examination is recommended for preventive healthcare.
2. Women with increased risk (relative risk of three to six times greater than that of the general public) There is no clear evidence to suggest that ovarian cancer screening with currently available methods will result in a decrease in mortality from ovarian cancer. If, after careful consideration of risks and benefits, ovarian cancer screening with serum markers such as CA-125 and/or trans-vaginal ultrasound is to be pursued, it is recommended that such screening be done within the framework of research studies to evaluate the efficacy of this approach.
3. Women with inherited risk (relative risk more than six times greater than that of the general public) While it is not clear that ovarian cancer screening will result

in a decrease in the number of deaths in women at inherited risk, those who have mutations in ovarian cancer susceptibility genes should undergo ovarian cancer screening using a combination of trans-vaginal ultrasound and CA-125 testing. For women with mutations in BRCA1 or the mismatch repair genes, MLH1, MSH2, and MSH6, this screening should generally begin between ages 30 and 35. For women with mutations in BRCA2, ovarian cancer screening should be initiated between ages 35 and 40.

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