Is It Time To Implement Ovarian Cancer Screening ?

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Epidemiology

- Ovarian cancer is the leading cause of death from gynecologic malignancies
- Most of the cases (70%) are diagnosed at advanced stages due to lack of specific symptoms
  - Most (90%) of the cases are sporadic
  - 10% of the cases hereditary

Holschnider 2000

Factors increasing ovarian cancer

Factor	Relative risk
Family history	***5-7***
BRCA-1 mutation	***18-29***
BRCA-2 mutation	***16-19***
Lynch II/HNPCC	***6-7***
Infertility	2-5
Nulliparity	2-3
Late menopause (>50 y)	1.5-2
Early menarche (<12y)	1-1.5
Smoking	1.5

Factrors decreasing ovarian cancer

Factıor	Relative risk
Multiparity	0.4-0.9
Oral contraceptive pills usage 4 years 8 years 12 years	 0.6 0.5 0.4
Hysterectomy tubal ligation	0.4-0.6
Lactation	0.5
Prophyplactic oophorectomy	0.6

Family History

- Family history is strong risk factor
- Risk increases 3 fold in case of one patient in first degree relative (3-4%)
- If two or more relative has ovarian cancer or if one ovarian cancer relative less than 40 years old ovarian cancer risk is 7%
- If two first degree ovarian cances the risk is 35-40%

Nguyen 1994

Hereditary Ovarian Cancers

- 10% of the ovarian cancers are hereditary
  - *5% BRCA-1*
  - *3% BRCA-2*
  - *1% LYNCH-II*
  - *1% unknown*
- The age of the patients of the hereditary ovarian cancers is 10 years younger

Smith 2001

BIOLOGICAL BASIS FOR SCREENING

- Survival from ovarian cancer is related to the stage at diagnosis
  - 5 years survival rate
    - 90% stage I disease
    - 25% with distance metastasis
- 75% of the patients are diagnosed at advanced stages
- Mortality from ovarian cancer has decreased only slightly in the past 30 years

Barnholz-Sloan JS. Am J Obstet Gynecol 2003

RISKS AND BENEFITS OF SCREENING

- The potential benefit identify ovarian cancer at a more localized and curable stage, reduced mortality
- The potential risks of a positive screening results with surgery Invasive procedures are associated with physical and psychological morbidity,complications and financial costs
- Although ovarian cancer is an important cause of cancer death, its incidence and prevalence are relatively low. The false-positive screening tests might cause unnecessary surgery in a large number of healty women

SCREENING TESTS

- Screening protocol for ovarian cancer should have a positive predictive value of at least 10 percent
- A screening program that targets all women over age 50 would require a test with a specificity of at least 99.6 percent
- Screening methods
  - *Tumor markers*
  - *Ultrasonography*
  - *Pelvic examinations*
  - *Multimodal*

Tumor Markers

- Non-invasive,
- Easily repeated over time,
- Relatively inexpensive

CA-125

- Glycoprotein antigen, the most widely studied marker
- Elevated in approximately 50% in early stage disease and 80% in advanced stage
- However, the specificity of CA 125 is limited. CA 125 levels are elevated in approximately 1% of healthy women

Karlson KS. Ann Inter Med 1994

Conditions With Increased CA-125

- Endometriosis
- Uterine leiomyoma
- Cirrhosis with or without ascites
- Pelvic inflammatory disease
- Cancers of the endometrium, breast, lung, and pancreas
- Pleural or peritoneal fluid due to any cause

CA-125

- Studies of CA-125 focused upon **postmenopausa**l women, since menstrual cycle variations and the benign gynecologic conditions in **premenopausal women would result false-positive tests**

- **Asymptomatic postmenopausal** women found that an elevated CA 125 concentration (≥30 U/mL) was a powerful predictor of subsequent ovarian cancer risk (RR 35.9 at one year and 14.3 at five years)

Jakops IJ. BMJ 1996

Studies about CA-125

- Three large screening studies in Sweden and England showed that
  - *the specificity of a single CA 125 level for detection of ovarian neoplasms in postmenopausal women ranged from 98.6 to 99.4 percent,*
  - *resulting with an unacceptably low positive predictive value of 3 percent*

Zurawski WR. Int J cancer 1988
Einhorn N Obstet Gynecol 1992
Jacops I. BMJ 1993

Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) trial

- 78,237 healthy women between 55 and 74 years of age were randomly assigned to screening and control groups;
- 39,115 women were assigned to screening with annual CA 125 and annual transvaginal ultrasound.
- Data from the baseline prevalence screen in 28,816 women found an **abnormal CA 125 in 436 women (1.5 percent);** the positive predictive value for invasive cancer was 3.7 percent
- At four years of follow-up, the positivity rates of CA-125 remained essentially unchanged from baseline and the positive predictive value was 2.6 percent

Human Epididymis Protein 4: HE4

- Similar sensitivity to CA 125 when comparing serum from *ovarian cancer cases to* ***healthy controls***
- Higher sensitivity when comparing ovarian cancer cases to **benign gynecologic disease**
- In a study of 531 women with pelvic masses, an algorithm using HE4 and CA 125 correctly classified 93.8 percent of cases of epithelial ovarian cancer as high risk

Clarke-Peasron DL. N Eng J Med 2009

Combination of Tumor Markers (CA 125, HE4, CEA, and VCAM-1)

- 2031 healthy women and 1067 women with early and late stage ovarian cancers, benign pelvic tumors, or breast, colorectal, or lung cancer
- **A four-marker panel** (CA 125, HE4, CEA, and VCAM-1) had the highest diagnostic power, with 86 percent sensitivity for early-stage ovarian cancer at 98 percent specificity.
- Combinations of biomarkers **may provide improved detection** as the first step in a multimodal screening protocol.

Yurkovetsky Z. J Clin Oncol 2010

Other tumor markers

- To determine the potential benefit of biomarkers, it is important that they can discriminate disease **before it is clinically diagnosed.**
- In a case-control study three tumor markers **(CA 125, mesothelin, and HE4)** began to increase three years before the diagnosis of ovarian cancer.
- CA 125 was most strongly predictive of ovarian cancer, with evidence for some incremental contribution of HE4 and mesothelin to risk prediction

Anderson GL. J Natl Cancer Inst 2010
Moore LE. Cancer 2012

Pelvic ultrasonography

- Pelvic ultrasonograhy has been evaluated as potential first-line screening methods for ovarian cancer
- **Transvaginal ultrasonography** allows better visualization of the ovaries
- With ultrasonography the size, morphologic characteristics (presence of septae or cyst wall irregularity) can be evaluated
- Ultrasound has the
  - sensitivity of 80-100%
  - specificity of 94 to 99 percent in screening studies

Karlan BY. Am J Obstet Gynecol 1993

Pelvic Ultrasonography: Lower-risk women

- Compared with high risk women for ovarian cancer, ultrasonography in **women at lower risk have more favorable results.**
- The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS), the largest study 202,638 postmenopausal women aged 50 to 74 ransomized to **no screening**, annual **TV-US**, or **multimodal** screening (CA 125 followed by TVUS if CA 125 abnormal).
- After 11 years of follow-up ovarian cancer was diagnosed in 314 (0.6 percent) of women in the TVUS arm, **and there was no significant mortality reduction compared with no screening**

Menon U. Lancet Oncol 2009
UKCTOCS Trial. Lancet 2016

Pelvic ultrasonography: High-risk women

- In this group screening studies with ultrasonography has performed poorly in detecting **early-stage epithelial ovarian cancer**

- 12,709 high risk patients's scans were performed:
  - all ovarian, peritoneal, and fallopian tubal cancers detected by ultrasonography during the screening period were stage III;
  - **no early stage disease was identified.**

Fishman DA. Am J Obstet Gynecol 2005

Pelvic Exam

- Routine pelvic examination for ovarian cancer screening is not recommended
  - Early stage tumors are rarely found due to the deep anatomic location of the ovary.
  - Tumors detected by bimanual pelvic examination are usually at an advanced stage and associated with a poor prognosis
  -
- A review of 52 studies found no data to support the use of the pelvic examination in asymptomatic, average-risk women

Smith LH. Obstet Gynecol Surv 1984
Bloomfield HE. Ann Intern Med 2014

Multimodal Screening

Randomized trials have evaluated combination screening with serum CA 125 and ultrasonography, either performed sequentially

- *The Shizuoka Cohort Study of Ovarian Cancer Screening (83.000 women) -- 2008*
- *Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) trial (68.557 women)---2011*
- *The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) ((202.638 women) --- 2016*

The Shizuoka Cohort Study of Ovarian Cancer Screening

- 83.000 postmenopausal women randomized pelvic USG, CA-125 and control group (9.2 years)
- There was **no significant difference** in the detection of ovarian cancer (27 vs 32)
- There was a **non-significant trend toward earlier-stage disease** in the screened group
- **Mortality data** is not available

Kobayashi H. Int J Gynecol Cancer 2008

Prostate, Lung, Colorectal, and Ovarian Cancer Screening (PLCO) trial

- 68,557 postmenopausal women (aged 55 to 74 years) were ramdomized screening and control (6 years)
- Primary outcome was cancer mortality
- Ovarian cancer detection rate was was similar in each group (5.7 versus 4.7 per 10,000 person-years)
- There was no difference in the stage of ovarian cancer, between the groups (%77-78 stage III-IV respectively)
- Screening did not reduce mortality

Buys SS. Am J Obstet Gynecol 2005
Buys SS Jama 2011

The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS)

- L**argest randomized trial using** of CA- 125 and TVUS
- 202,638 postmenopausal women aged 50 to 74 years annual **TVUS**, or **multimodal** screening (MMS) to **no screening**
- The 50,640 patients in the MMS arm received annual screening with CA 125, followed by TVUS if the CA 125 was abnormal
  - After a median follow up of 11 years, there were
  - MMS cancer 0.7% death 0.29% , mortality reduction %15
  - USG cancer 0.6% ,death 0.30% , mortality reduction %11
  - Control cancer 0.6% death 0.34%
- Compared with no screening, MMS detected cancer at an earlier stage (I, II, and IIIa) (26 percent versus 39 percent).

Jacops J. UKCTOCS . Lancet 2016

The UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) -2

- The primary analysis showed a nonsignificant trend toward a 15 percent reduction in mortality from ovarian cancer.
- Mortality rate was not different inital years but they found encouraging evidence of a mortality reduction in years 7–14,
- It is estimated that 641 women would need to be screened annually for 14 years to prevent one death from ovarian cancer.

High Risk Women

- No randomized trials of screening for women with a familial ovarian cancer syndrome, since no control group
- Multimodal screening in women at high risk due to a genetic predisposition or family history have been largely disappointing
- United Kingdom Familial Ovarian Cancer Screen Study (UK FOCSS)
  - 3563 women with familial ovarian cancer screened with CA-125 and USG
  - Detection rate is 81-87%, 30.8% of the patients were stage I-II

Rosenthal AN. J Clin Oncol 2013

High Risk Women

- Women **who had not been screened** in the year before cancer diagnosis were more likely to have stage IIIc or higher cancer (85% vs-26%)
- Although **Risk reducing surgery** remains the only reliable method of decreasing mortality, this study suggests that screening may have the potential reduce risk for women who wish to maintain their childbearing potential
- **Other studies** of screening in women at high-risk have shown less favorable results, with most cases at late stage at the time of screen detection

SYNTHESIS OF THE EVIDENCE AND APPROACH TO SCREENING
(Women at Average risk)

- Screening for ovarian cancer with CA 125 or ultrasound is not recommended for premenopausal and postmenopausal women without a family history of ovarian cancer

- Based on the available data, it is not clear that the benefits of screening for ovarian cancer outweigh the harms related to the adverse effects related to false positive findings

Women at increased Risk

- Lower risk famil history (isolated family member with ovarian cancer)
  - *Should be counselled about their individual risk*
  - *There is no evidence to support screening in this group, screening should be based on individualized considerations involving the patient and clinician*
- High risk family history (Hereditary ovarian cancer syndrome)
  - *Should be referred to genetic counselling*
  - *For women with a BRCA mutation, risk-reducing salpingo-oophorectomy (BSO) is indicated by age 35 to 40 and when childbearing is completed*
  - *BSO is also indicated for carriers who are diagnosed*
  - *Oral contraceptive use in BRCA mutation carriers decreases the risk of ovarian cancer with early-stage breast cancer.*

RECOMMENDATIONS OF EXPERT GROUPS

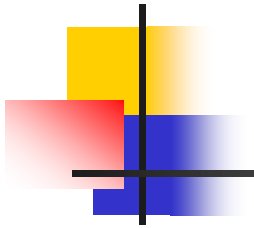
- No North American expert groups recommend routine screening for ovarian cancer
- For women with identified hereditary ovarian cancer syndromes **SGO and the (NCCN)** recommend screening every six months with CA 125 and TV-US beginning between the ages of 30 and 35 years or 5 to 10 years earlier than the earliest age of first diagnosis of ovarian cancer in the family
- **ACOG** states that there is no evidence that screening improves survival in women in high-risk populations,
- **The National Cancer Institute** finds there is not sufficient evidence to support screening for ovarian cancer in any population, including women at increased risk

SUMMARY AND RECOMMENDATIONS

- **Survival** for ovarian cancer is related to stage . However, most ovarian cancers are diagnosed at advanced stage
- The strongest known risk factor for ovarian cancer is a family history. Familial ovarian cancer syndromes (the Lynch syndrome and breast-ovarian cancer syndromes related to BRCA1 or BRCA2 mutations) occur rarely, but present much greater risk than a sporadic family history of ovarian cancer
- CA 125, the most widely studied tumor marker for ovarian cancer screening, and elevated in 50 to 90 percent of women with early ovarian cancer, but also can be elevated in numerous other conditions.
- Ca-125 alone is not recommended in screening in average-risk women (Grade 1B).

SUMMARY AND RECOMMENDATIONS-2

- Serial measurements of **CA 125**, using an algorithm that incorporates age and rate of change may improve the positive predictive value of screening, but not sufficiently to incorporate into clinical practice at this time
- **Transvaginal ultrasonography** (TVUS), when used alone in screening, has not been effective in identifying early-stage cancer
- Average-risk women is not suggested to screen for ovarian cancer (Grade 2B).
- For women with a family history of ovarian cancer who do not have a confirmed ovarian cancer syndrome, we suggest management as for women at average risk (Grade 2C).
- *For familial ovarian cancer patients risk reducing surgery is indicated by age 35 to 40 and when childbearing is completed*



THANK YOU FOR YOUR ATTENTION

BRCA-1 Mutation

- BRCA genes are involved in the repair of chromosomal damage
- If these genes are damaged by a BRCA mutation, damaged DNA is not repaired properly, and this increases the risk for cancer

- BRCA-1 gene is located in the long arm of the chromosome 17
- BRCA-1 mutationa carriers have the risk of 30-40% of ovarian cancer developing
- BRCA-1 mutation is seen 1/800 frequency and with **otosomal dominat** pattern

BRCA-2 Mutation

- Constitutes 3% of the ovarian cancer
- Located in the long arm of the chromosme 13
- ovarian cancer is about 25% for women with BRCA2 mutations.[49]

Ovarian Cancer Frequency

	Frequency	Mortality
All cancers	5	4
Gynecological Cancers	2	1

Tortolero 1995

Studies about CA-125

- The change in CA 125 levels over time is a more promising screening method.
- A large prospective study in 9233 postmenopausal women, with measurements of Ca- 125 at two or more times, used a modeling method to estimate risk of ovarian cancer The model incorporates age-specific incidence of cancer, absolute CA 125 level, and rate of change over time. Compared with a specific cutoff value of CA 125, the model improved sensitivity for detection of ovarian cancer from 62 to 86 percent when specificity was fixed at 98 percent.
- An algorithm incorporating change in CA 125 measurements over time was used in the UK Collaborative Trial of Ovarian Cancer Screening