OVARIAN CANCER

Updates in Screening, Early Detection and Prevention

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OVARIAN CANCER EPIDEMIOLOGY

2016 ACS Statistics

- 21,500 new cases
- 14,600 deaths
- Over **70%** present with Stage III/IV
- **15-30%** 5-year survival

OVARIAN CANCER RISK FACTORS

Genetic Mutations	*Lifetime Risk*
BRCA1	35–60%
BRCA2	10–30%
LYNCH	10–12%
RAD51 c/d	9–10%
PALB2	10%
BRIP1, ATM	5%
Family hx, no mutation	5%

INCREASING RISK

	Relative Risk
HRT	1.20–1.5
Obesity	1.07–1.13
Endometriosis	1.19-1.71
Talcum powder	Conflicting results
Dietary	No association
Infertility drugs	No association

DECREASING RISK

	Hazard Ratio (95% CI)
Tubal ligation	0.75 *(0.66–0.82)*
Oral contraceptives	0.78 (5 yrs), *0.64* (10 yrs), *0.56* (15 yrs)
Breastfeeding	0.76 *(0.69–0.83)*
Hysterectomy	0.79 *(0.70–0.88)*
Salpingectomy	0.65 *(0.52–0.81)*
BSO ± hysterectomy	0.06 *(0.03–0.12)*
Multiparity	0.70 *(0.50–0.85)*

SCREENING CHALLENGES

Ovarian Cancer

- Annual incidence: 40/100,000 women
  — 1 cancer per 2,500
- Major surgical procedure required for diagnosis
  — Even a 1% false ⊕ results in 25 surgeries per case of cancer

MULTIMODALITY SCREENING

PLCO Screening Trial

- Enrolled 78,232 women from 1993–2001
- Age 55–74
- Randomized to annual TVS/CA125 vs routine care
- Baseline analysis of 28,816 women randomized to screening:
  - CA125 ↑ in 1.5% (PPV for cancer 3.7%)
  - TVS abnormal in 4.7% (PPV 1.0%)

FINAL RESULTS

PLCO Screening Trial

- 39,105 received screening:
  - CA125 x 6 yrs
  - TVS x 4 yrs
- 39,111 got usual care

Follow-up at 13 years:

- No difference in ovarian cancer mortality between screened and usual care patients
- Of patients with a false positive screen who underwent surgery, 15% suffered a significant complication

Jama 2011

PREVALENCE SCREEN

UK Collaborative Trial of Ovarian Cancer Screening

202,638 post-menopausal women enrolled:

- Controls
- Annual CA125 (using risk of Ov Ca algorithm), followed by TVS (MMS)
- Annual TVS (TVS)

UKCTOCS trial

UK Collaborative trial for ovarian cancer screening

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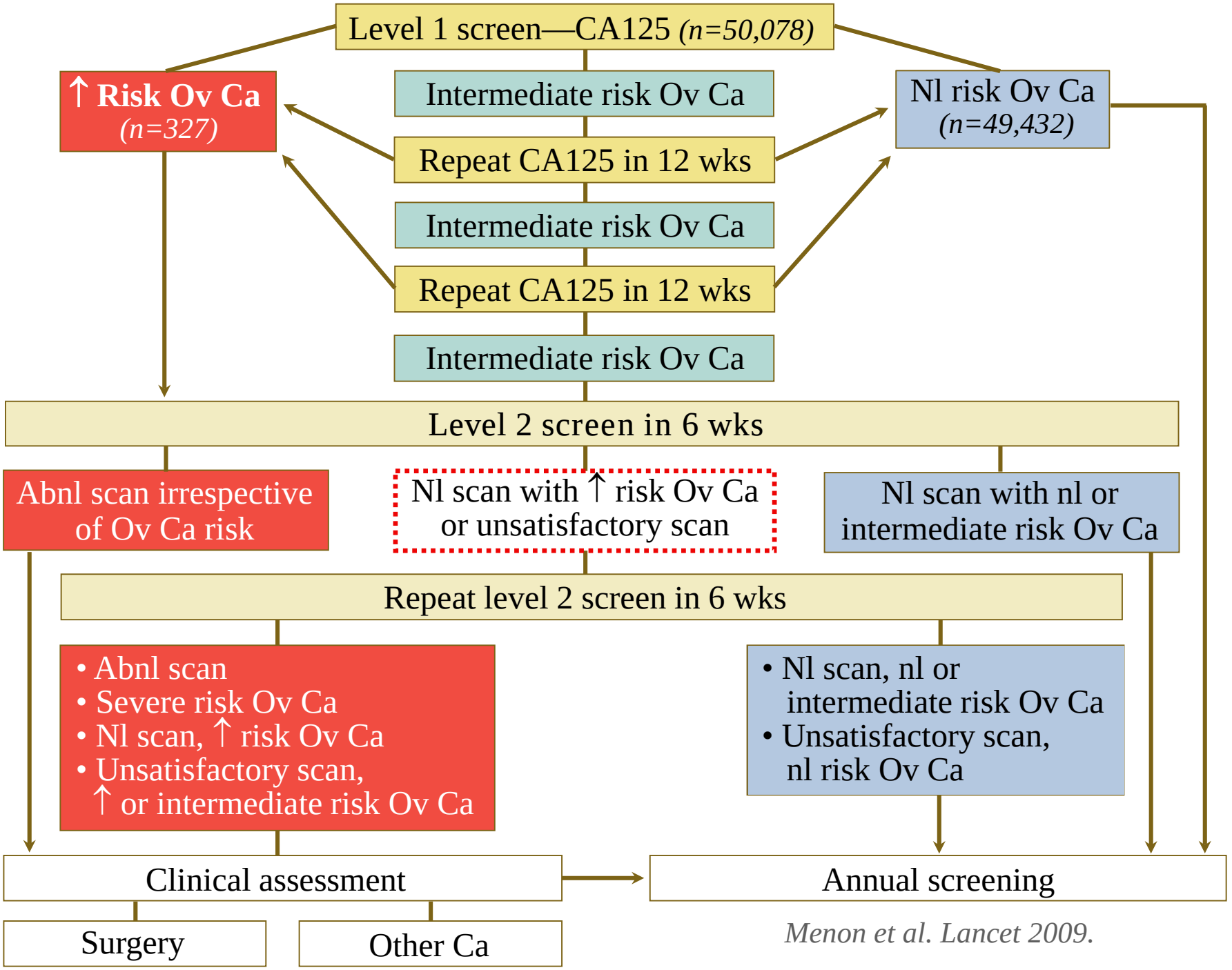

Menon et al. Lancet 2009.

RESULTS

UKCTOCS Multimodal Arm

Sensitivity: **85.8%** *(79.3–90.9%)*

Specificity: **99.8%** *(99.3–99.9%)*

Positive Predictive Value: **20.8%** *(17.7–24.1%)*

Operations per Case OC: **4.8**

ROCA screening strategy with TVS as a secondary screen (MMS) detects twice as many ovarian cancers as a single cut-off value

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RESULTS

UKCTOCS Ultrasound Arm Screening Performance

Sensitivity: **62.1%** *(52.9–70.7%)*

Specificity: **99.7%** *(99.7–99.7%)*

Positive Predictive Value: **8.1%** *(6.5–10.10%)*

Operations per Case OC: **12.3**

UKCTOCS FINAL RESULTS

Effect of Screening on Ovarian Cancer Mortality

- **Ovarian Cancer Deaths**

Controls *(N=101,359)*	347
MMS *(N=50,640)*	148
U/S *(N=50,639)*	154

- **Mortality Reduction**

MMS	15% *(-3 to 30, p=0.10)*
U/S	11% *(-7 to 27, p=0.21)*

- Higher reduction in mortality after screening had stopped
- Exclusion of prevalent cases (years 0-7) yielded a 20% reduction in death for MMS (p=0.02)

Jacobs, Lancet 2016

ANNUAL CA125 AND TVS

Screening of High-Risk Populations

- Prospective screening of 888 BRCA1/2 mutation carriers *(Netherlands 2007)*

5/10 cancers not screen detected
8/10 cancers Stage III/IV

- Prospective screening of 179 BRCA1/2 mutation carriers *(UK 2007)*

Sensitivity: 50%
Specificity: 82.8%

PPV: 1.3%
NPV: 99.7%

UKFOCSS

UKFOCSS
UK Familial Ovarian Cancer Screening Study
2002-2010

- 4,531 women with >10% lifetime risk of ovarian cancer
- CA125 q 4 mos (ROCA), followed by TVS if abnormal
- 19 cancers detected during screening study
- 162 + screens, 13 cancers, 149 false + surgeries
- Of 13 screen-detected cancers, 5 (38%) were stage I & II and 12 of 13 had R0

CONCLUSION	ROCA testing every 4 mos a reasonable option but should not replace RRSO

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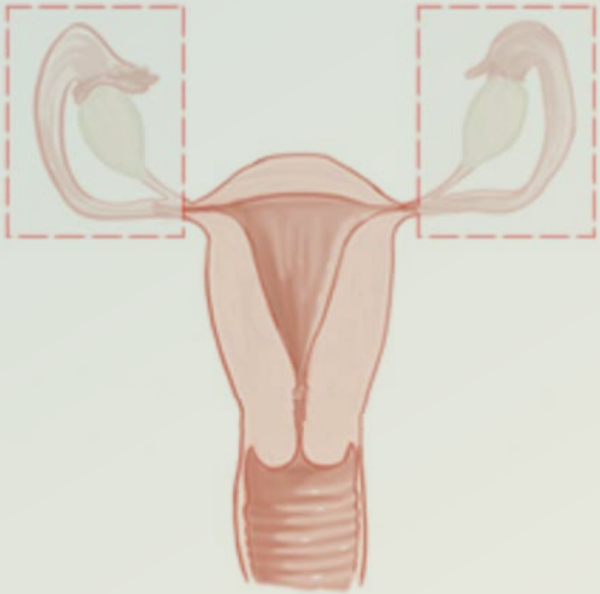
RECOMMENDATIONS FOR HIGH-RISK WOMEN

Ovarian Cancer

- BSO when childbearing complete
- For those not ready, or unwilling, to undergo BSO, enrollment into clinical trials for screening should be encouraged
- Some consideration for salpingectomy first



RECOMMENDATIONS

- Ovarian cancer screening, Grade D:
  — Fair evidence to recommend exclusion from periodic health exam
- Genetic testing, Grade B:
  — Fair evidence to recommend in those with a family hx

OVARIAN CANCER DIAGNOSIS

ACOG and SGO

- Clinicians should have a high index of suspicion in a symptomatic patient
- Educating women and practitioners about symptoms and promptly initiating follow-up is currently the best method of diagnosis

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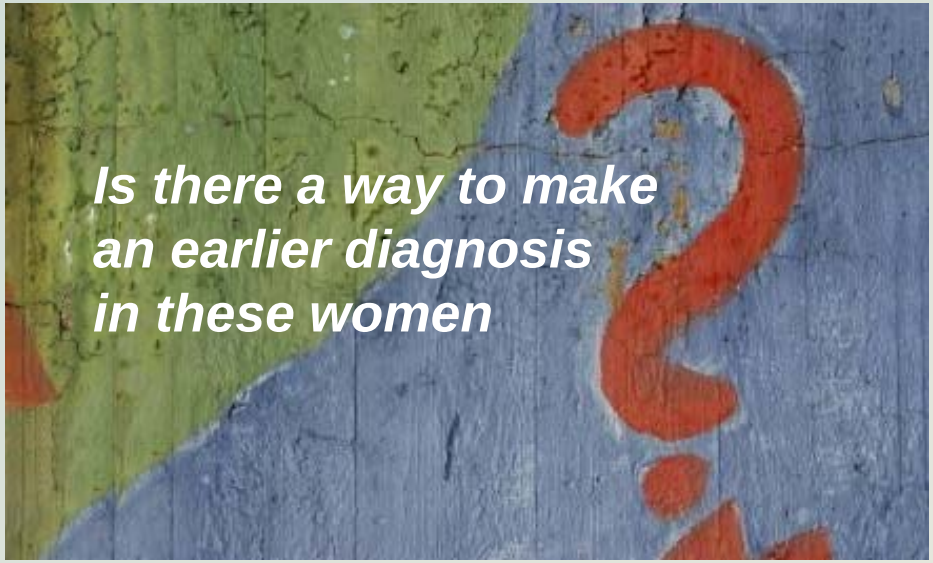
QUESTION

Ovarian Cancer

- Currently, screening not recommended for general population
- 80% of ovarian cancers occur in women without a family history



OVARIAN CANCER DIAGNOSIS

Goals of National Survey

- To conduct large national survey of women with ovarian cancer
- To evaluate preoperative symptoms which patients experience
- To evaluate potential causes in delayed diagnosis

Goff, Muntz, Mandel, Melancon. Cancer 2000.

SYMPTOMS OF OVARIAN CANCER

- 1,725 women with ovarian cancer surveyed
- 95% had symptoms:
  - Abdominal/GI **most** common
  - Pelvic symptoms **least** common
- 89% of women with Stage I/II disease had symptoms

Goff BA, et al. Cancer 2000.

DURATION OF SYMPTOMS

Ovarian Cancer Diagnosis

Months	
0–2	30%
3–6	35%
7–12	20%
>12	15%

RESULTS

Ovarian Cancer Diagnoses

- Initial diagnosis:
  - Irritable bowel 15%
  - Nothing 13%
  - Stress 12%
  - Gastritis 9%
  - Constipation 6%
  - Depression 6%
  - Other 47%
- Treated for another condition 30%

CONCLUSIONS

Ovarian Cancer Diagnosis

- Majority of women with ovarian cancer **DO** have symptoms
- Majority of women with early stage disease **DO** have symptoms
- Delays in diagnosis common

FREQUENCY OF OVARIAN CANCER SYMPTOMS

Women Presenting to Primary Care Clinics

- **GOAL:** To identify frequency, severity and duration of symptoms typically associated with ovarian cancer in a population of women presenting to primary care clinics *(n=1709)*
- Comparison was made to 128 women with masses who were surveyed about symptoms prior to surgery

Goff BA, et al. JAMA 2004.

ODDS RATIOS OF OVARIAN CANCER SYMPTOMS

Women With and Without Cancer

Symptoms	*Cancer vs. Clinic Patients*
Pelvic pain	**2.2** *(1.2–3.9)*
Abdominal pain	**2.3** *(1.2–4.4)*
Difficulty eating	**2.5** *(1.3–5.0)*
Bloating	**3.6** *(1.8–7.0)*
Abdominal size	**7.4** *(3.8–14.2)*
Urinary urgency	**2.5** *(1.3–4.8)*
Constipation	1.6 *(0.9–3.0)*
Fatigue	1.4 *(0.7–2.7)*

Excluding patients presenting for routine checkup or mammogram only.

MEDIAN # EPISODES EACH SYMPTOM / MONTH

Symptoms of Ovarian Cancer

Symptoms	*Malignant Ovar Mass (n=44)*	*Primary Care Clinic (n=1600)*	*P Value*
Pelvic pain	**24**	**2**	**0.001**
Abdom pain	**23**	**2**	**0.017**
Bloating	**30**	**2**	**0.004**
Fatigue	**30**	**8**	**0.001**
Urinary sx	**30**	**12**	**0.02**
Constipation	**12**	**2**	**0.001**
Diarrhea	6	2	0.06

MEDIAN DURATION EACH SYMPTOM IN MONTHS

Symptoms of Ovarian Cancer

Symptoms	*Malignant Ovar Mass (n=44)*	*Primary Care Clinic (n=1600)*	*P Value*
Pelvic pain	3	11	0.06
Abdom pain	5	11	0.05
Bloating	3	12	0.04
Urinary sx	3	13	0.13
Constipation	3.5	12	0.001
Diarrhea	5	12	0.001
Fatigue	3	12	0.08

POSSIBILITIES FOR EARLIER DETECTION

Development of Ovarian Cancer Symptom Index

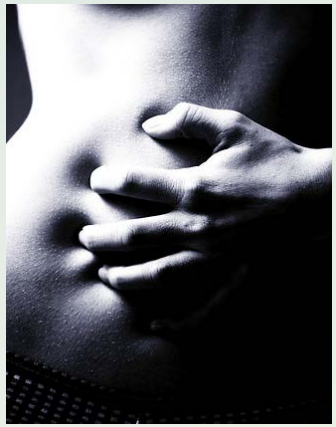
- Prospective case-control study
  - 149 with ovarian cancer
  - 488 controls
- Evaluated symptoms
  - Type
  - Frequency
  - Severity
  - Duration

Goff et al. Cancer 2007.

POSSIBILITIES FOR EARLIER DETECTION

Development of Ovarian Cancer Symptom Index

- Index considered positive
  - Abdominal/pelvic pain
  - ↑ Abdominal size/bloating
  - Difficulty eating/feeling full
- If present <1 year and occurred >12 days/month



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Goff et al. Cancer 2007.

POSSIBILITIES FOR EARLIER DETECTION

Performance of Symptom Index

		Sensitivity	*Specificity*
• Age:	<50	66.7%	90.0%
	≥50	86.7%	86.7%
• Disease stage:	Early	57.7%	
	Late	87.0%	

- Percent testing positive:
  - General population 45/1,709 (2.6%)
  - Age 50+ 8/560 (1.4%)
  - Age <50 33/1,102 (3.3%)

CONCERNS RE SYMPTOM-BASED SCREENING

Ovarian Cancer Diagnosis

CAUSE

- Cancer worry in women
- Difficulty with physician office visits
- High rates of unnecessary surgery with secondary complications

GOAL *To determine potential harms and patient/provider satisfaction with symptom triggered screening for ovarian cancer*

SYMPTOM-BASED SCREENING

Methods

- **7/08 – 7/11:** Women age 40+ enrolled from primary care clinics at UWMC (Women's, IM, FM)
- Exclusions: Pregnancy, BSO, unable to give consent
- Women filled out baseline health info and SI

IF SI POSITIVE

Women offered a **TVS** and **CA125**, then managed according to standard of care

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OVARIAN CANCER

Symptom-Triggered Screening

- Pilot study of 2,261 women found high level of satisfaction for patients and providers
- 5,014 women over age 40 screened with Symptom Index—**4.8%** ⊕
- TVS and CA125, if SI positive
  - — Tests performed secondary to screening
    - 8 endo bx
    - 3 laparoscopies
    - 1 hysteroscopy
    - 1 TAH-BSO

False positive rate for laparotomy/laparoscopy **0.08%**

Gyn Onc 2011.

SYMPTOM-TRIGGERED SCREENING

All OVARIAN CANCER Outcomes *(n=6015)*
8 Ovarian Cancers: Dx 31–843 days post-enrollment

2

Diagnosis within 6 months of Symptom Index
- SI+ 31 days (distant)
- SI− 78 days surgery for high-risk family history (stage IA)

6

Diagnosis 281–843 days post SI (mean 569)
- – All 6 SI− at time of study
- – 3 Regional
- – 3 Distant

DIAGNOSING OVARIAN CANCER EARLY

DOvE Study

- May 2008–April 2011:
  Women 50+ with sx of ovarian cancer enrolled
- CA125 and TVS performed within 2 weeks
- Intermediate CA125 repeated in 4 weeks
- Normal CA125 repeated in 4 mos
- DOvE patients compared with Ov Ca patients in the general clinic population of Montreal

Gilbert et al. Lancet Oncology 2012.

DOvE STUDY

Results

- Of 1,455 women enrolled, 11 cases of ovarian cancer or 1 in 132 women:
  - Stage I/II 4 (36%)
  - Small volume stage III 4 (36%)
  - Advanced stage suboptimal 3 (27%)
- 5 cases identified from follow-up CA125 only
- In clinic population, 56% suboptimal
- In addition, 11 uterine cancers detected
- Overall, 1 in 66 women diagnosed with GYN cancer

COMBINING SYMPTOMS & TUMOR MARKERS

Predicting Cancer in Women with Pelvic Masses

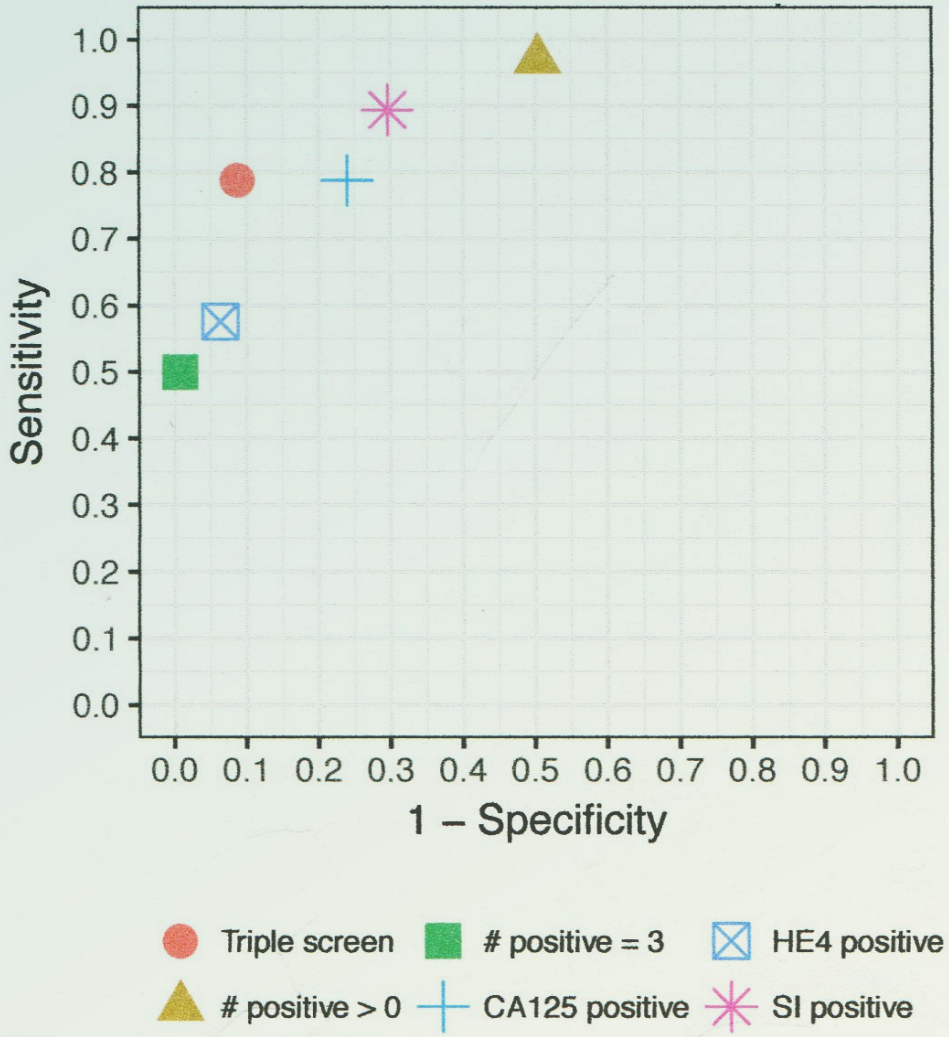
- 218 women with pelvic mass:
  - 66 ovarian cancer
  - 17 Borderline
  - 11 Metastatic
  - 124 Benign
- CA125, HE4, SI evaluated—
  tests are positive for sensitivity, specificity, PPV and NPV for combinations
- In 66 OC patients:

SI+	**87.9%**
CA125+	**74.2%**
HE4+	**60.6%**

Goff BA, et al. Gyn Onc 2017.

SENSITIVITY and SPECIFICITY

of the triple screen, each of its components, and for 3/3,2/3 or 1/3 components, positive to discriminate between ovarian cancers and benign ovarian tumors



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NEW DIRECTIONS

Ovarian Cancer Screening

- **A)** Urine markers
- **B)** Molecular alterations on Pap
- **C)** Circulating tumor DNA

PREVENTION OF OVARIAN CANCER

OCPs:	• General and high-risk populations
Tubal Ligation:	• General and high-risk populations
BSO:	• Recommended in high-risk populations • Detrimental in general population
Salpingectomy:	• Consider in general population • Unknown safety in high-risk population
Genetic Testing:	• All cancer patients • Significant family history

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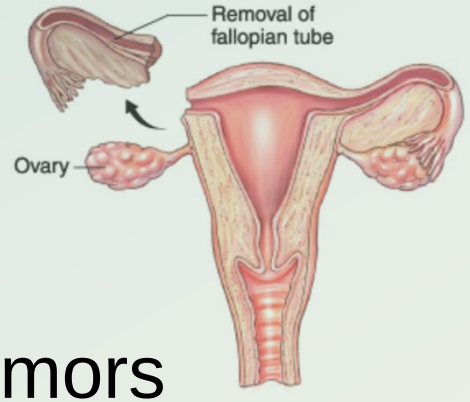
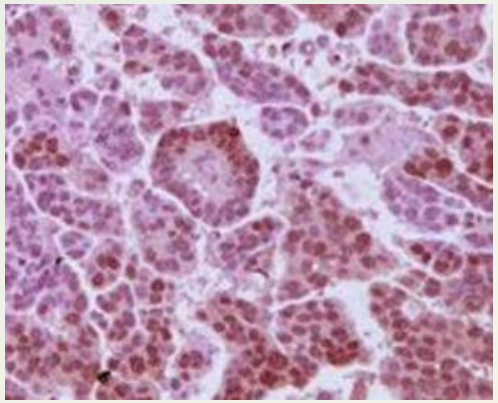
OPPORTUNISTIC SALPINGECTOMY

Rationale



- High-grade serous tumors account for 70% of epithelial ovarian cancer
- The majority of high-grade serous tumors have precursor lesions in the fallopian tube
- Removal of fallopian tubes at time of other surgery (opportunistic) could reduce high-grade serous tumors by 80–90%
- Allows retention of hormonally active ovaries



SALPINGECTOMY STUDIES

Low-Risk Patients

- Feasible—adds 13–16 mins. to surgical time
  (McAlpine. AJOG 2014)
- No difference in LOS, hemoglobin levels, surgical complications, return to normal function *(Walker JL. AJOG 2015)*
- No difference in ovarian function, as measured by hormonal levels or Doppler blood flow to ovaries
  (Walker JL. AJOG 2015)
- Single population-based study from Sweden:
  - HR 0.65 *(95% CI 0.52–0.81)*
  - Protection for bilateral salpingectomy; ~2X for unilateral
  (Yeon SH. Eur J Cancer 2016)
- In modeling, cost effective at lap hyst & sterilization
  (Dilley. Gyn Onc 2017)

SALPINGECTOMY

Low-Risk Patients

ACOG and SGO recommend discussion of opportunistic salpingectomy in all surgical patients who have com-pleted their fertility

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RISK-REDUCING BILATERAL SALPINGECTOMY

Until Bilateral Oophorectomy in High-Risk Women

- No data on safety
- No protection from breast cancer risk
- Offered to women who refuse RRSO
- 30% of **FORCE** patients would be willing to participate in a clinical trial

FORCE
Facing Our Risk of Cancer Empowered
Fighting Hereditary Breast and Ovarian Cancer

- **SU2C–WISP** Trial *(**W**omen choosing **S**urgical **P**revention)* (ongoing to compare outcomes of BS vs BSO)

SU2C
STAND UP TO CANCER

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CONCLUSIONS

Early Detection of Ovarian Cancer

- No effective screening test currently available
- Early diagnosis relies on symptom recognition by patients and practitioners
- Prevention strategies, including opportunistic salpingectomy, can significantly reduce the risk of ovarian cancer