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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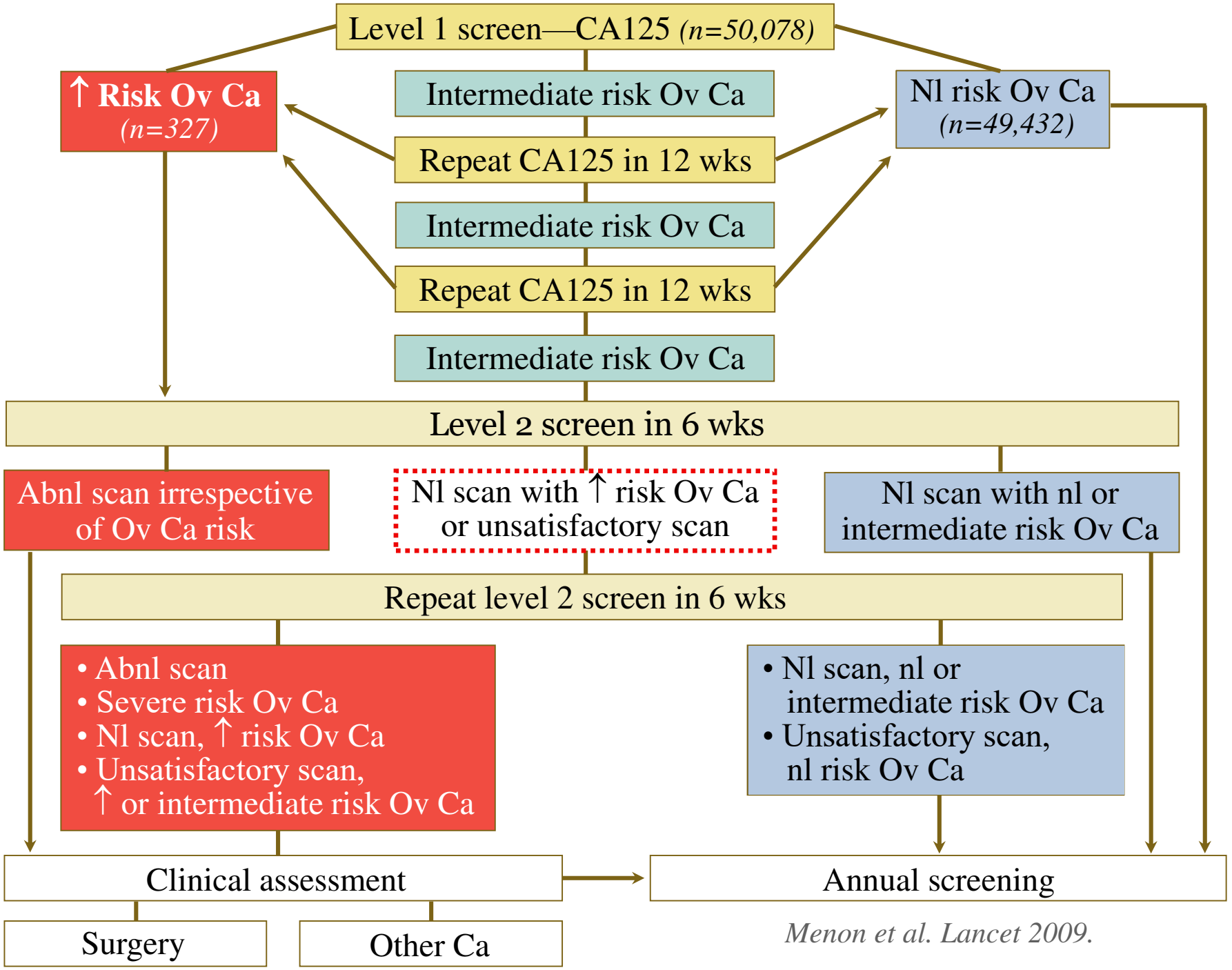

Menon et al. Lancet 2009.

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

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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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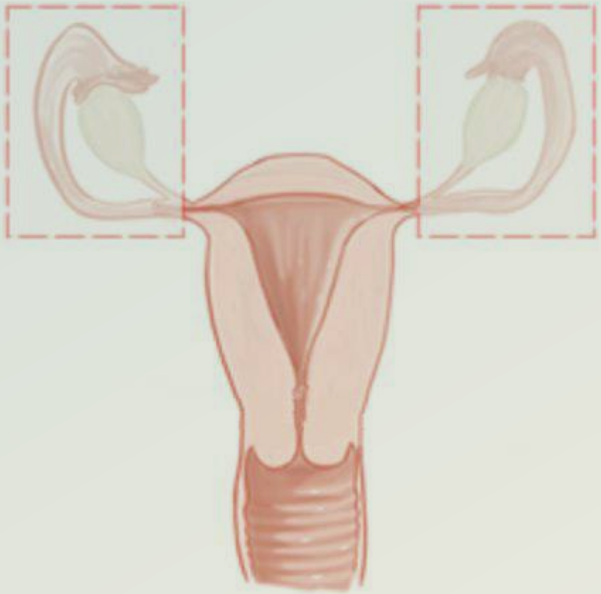
RECOMMENDATIONS FOR HIGH-RISK WOMEN

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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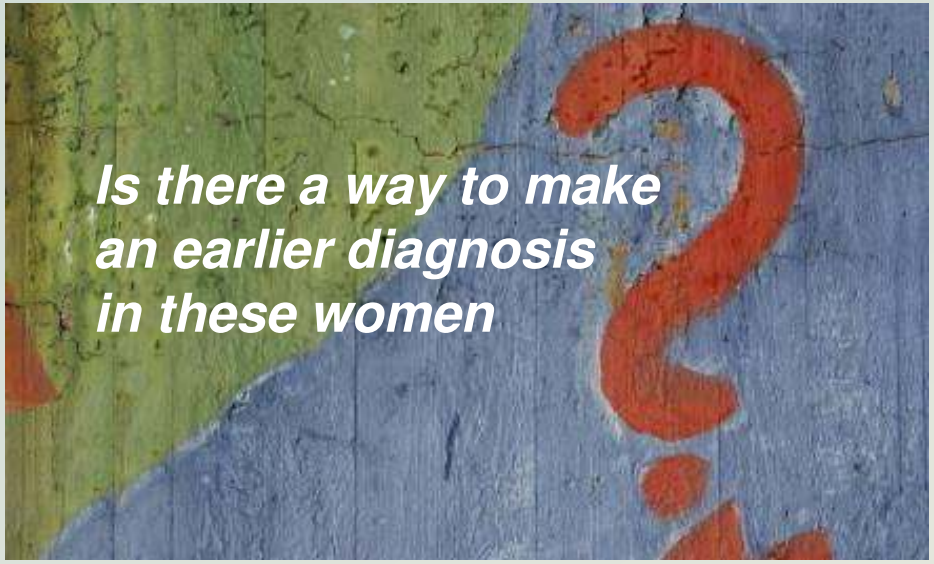
QUESTION

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=128)*	*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=128)*	*Primary Care Clinic (n=1600)*	*P Value*
Pelvic pain	**3**	**11**	**0.05**
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

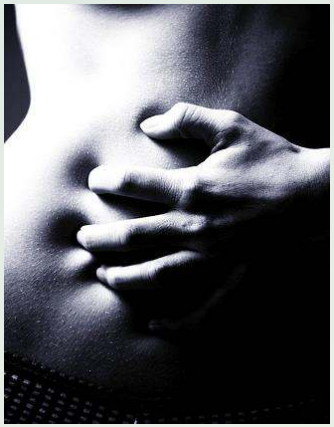
- **Prospective case-control study**
  - 149 with ovarian cancer
  - 488 controls
- **Evaluated symptoms**
  - Type
  - Frequency
  - Severity
  - Duration

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

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%**

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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**

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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**

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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

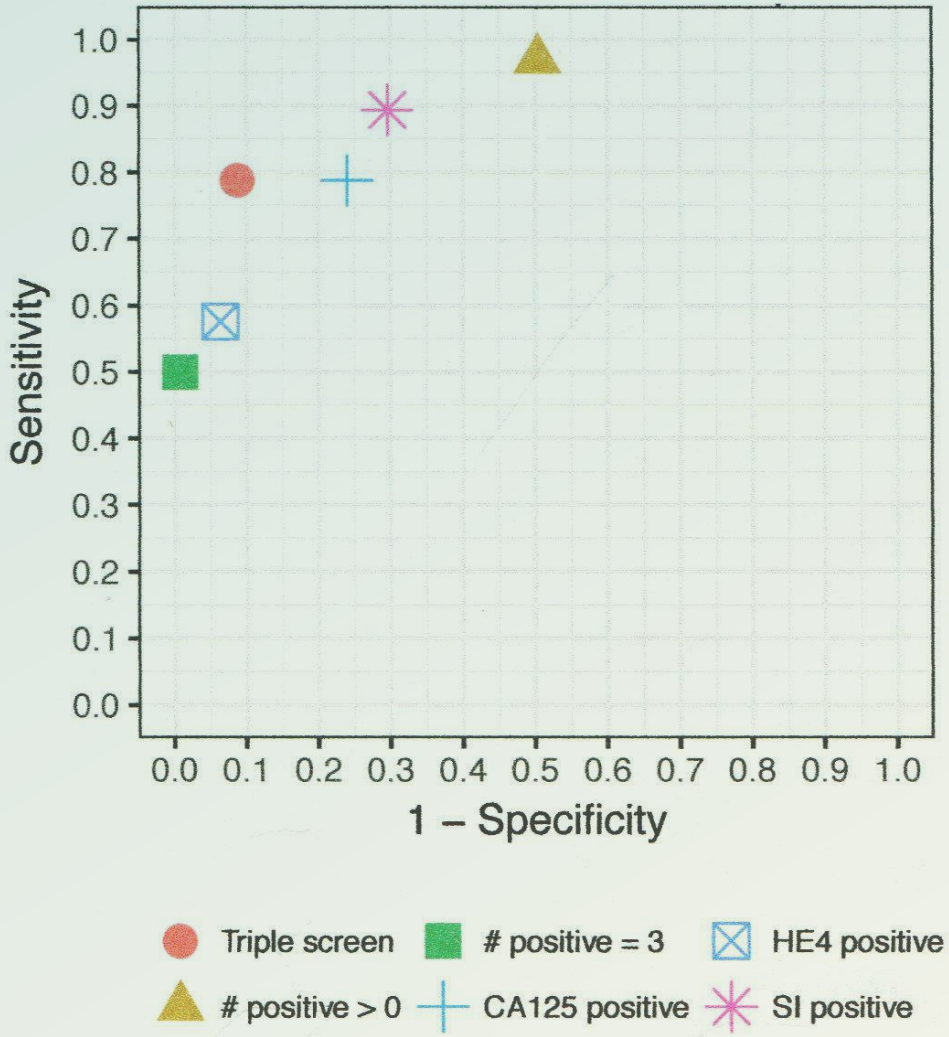
- **218 women with pelvic mass:**
  - 66 ovarian cancer
  - 17 Borderline
  - 11 Metastatic
  - 124 Benign
- **CA125, HE4, SI evaluated—tests are positive for sensitivity, specificity, PPV and NPV for combinations**
- **In 66 OC patients:**

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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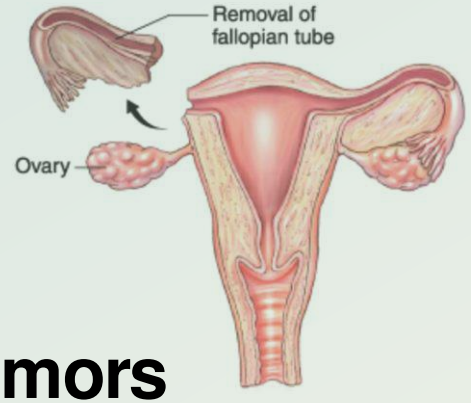
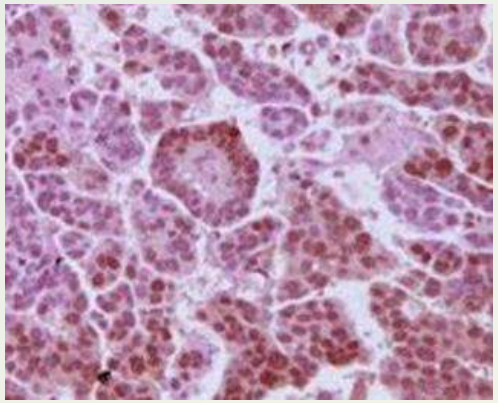
OPPORTUNISTIC SALPINGECTOMY

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 completed 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**