A Teaching Affiliate of Harvard Medical School

Update in Gynecologic Oncology for the Internist

Marcela G. del Carmen, MD, MPH
Professor
Obstetrics, Gynecology and Reproductive Biology
Harvard Medical School
President, MGPO

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

- No conflict of interests.

Objectives

- Early Detection Ovarian Cancer
  - Challenges
  - Ultrasound alone
  - Combination CA 125 and Ultrasound
- Genetic Screening/Testing

Background

- Worldwide 300,000 new cases/year
- 185,000 ovarian-cancer related deaths/year globally
- 3% of cancers among women in the US.
- Leading cause of death from gynecologic cancers.
  - 22,000 new cases/year in US
  - 14,000 cancer-related deaths/year in US
- Fifth leading cause of all cancer related deaths in women.
- Lifetime risk of invasive ovarian cancer is 1 in 71.
- Probability of a woman in the US developing ovarian cancer is less than 2%.

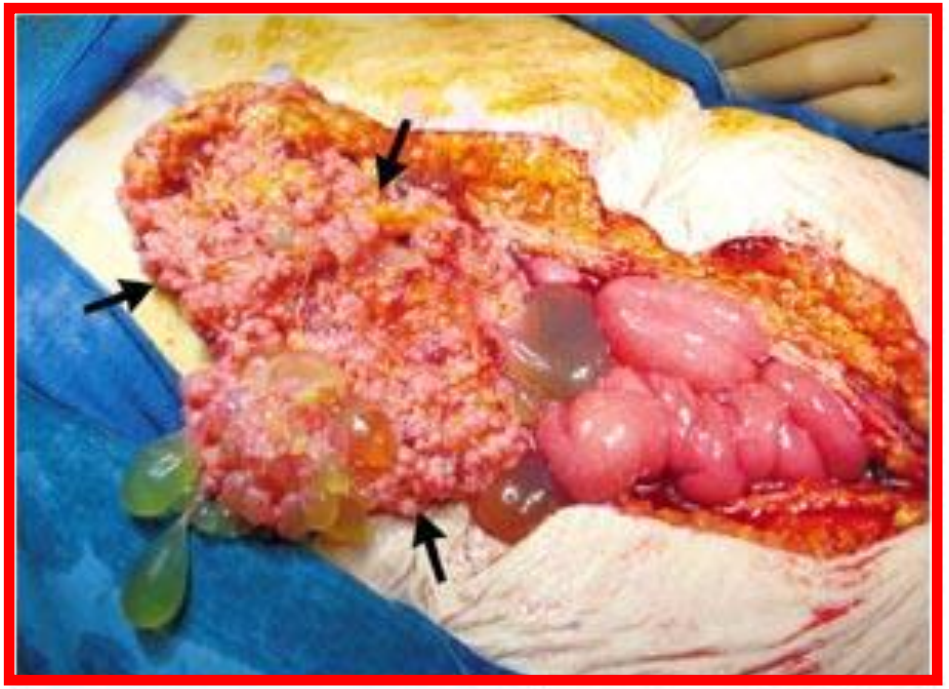
Siegel et al. CA Cancer J Clin 2018;68(1):7

Risk Factors

- Genetic predisposition
  - Family hx of ovarian cancer vs. Familial ovarian cancer syndromes
  - Family hx of ovarian cancer:
    - Meta-analysis showed lifetime probability of ovarian cancer in increases from 1.6 to 5% with one first/second degree relative with EOC
  - Familial ovarian cancer syndromes:
    - Lynch II/HNPCC Syndrome (3-14% risk ovarian cancer)
    - BRCA 1 and 2 (35-45% and 15-25% risk of ovarian cancer)
- Age
- Reproductive and endocrine factors

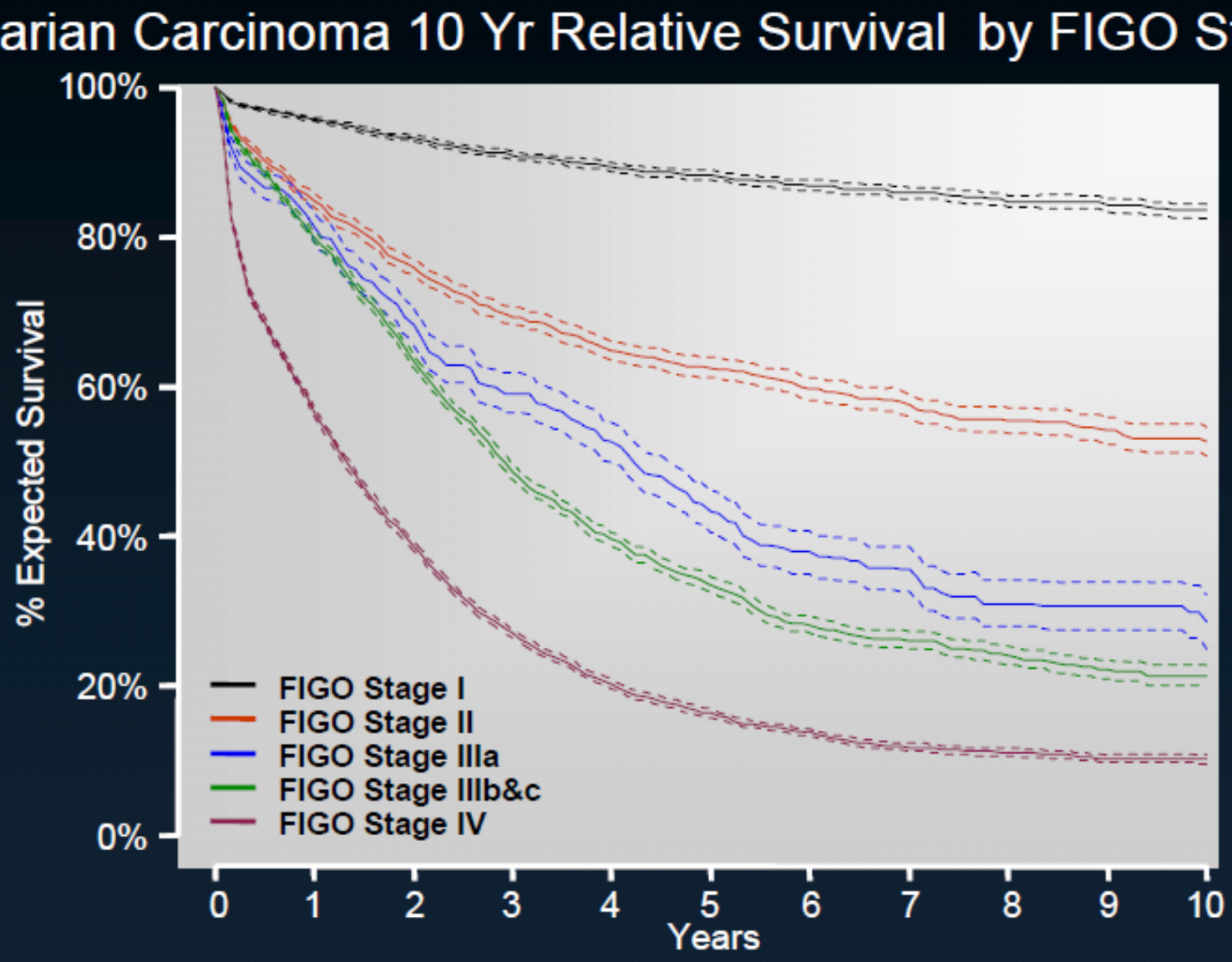
Poor prognosis in ovarian cancer

FIGO Stage	Percent (%)
I	24
II	6
III	55
IV	15



MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Ten-year Survival Is Best When Ovarian Cancer Is Confined to the Ovary at Diagnosis



Challenges

- Given the low prevalence of ovarian cancer (40 cases per year per 100,000 women), screening test must have both high sensitivity and high specificity.

- Require:
  - Sensitivity at least 75%
  - Specificity of more than 99.6%
  - To achieve a positive predictive value of 10%

Screened Population Features

1. Disease has a high enough **prevalence** to justify screening

2. Medical care available if screening test is positive

3. Patient is willing & able to undergo further evaluation

Issues Screening for Ovarian Cancer

- Failure to identify a histologic precursor lesion or a molecular event that precedes malignant transformation.
  - Ovarian cancer may develop from multiple foci within the abdomen

- Find a test that can detect not only clinically apparent ovarian cancer but also early disease long before it causes symptoms.

Objectives

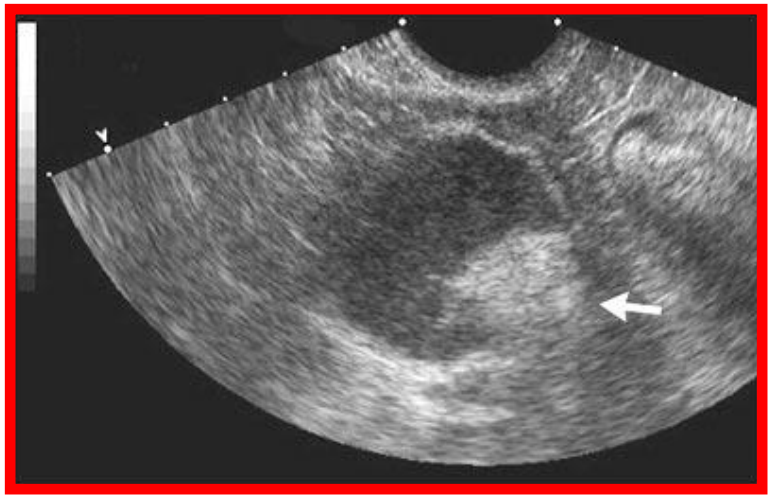
- Early Detection Ovarian Cancer
  - Challenges
  - *Ultrasound alone*
  - Combination CA 125 and Ultrasound

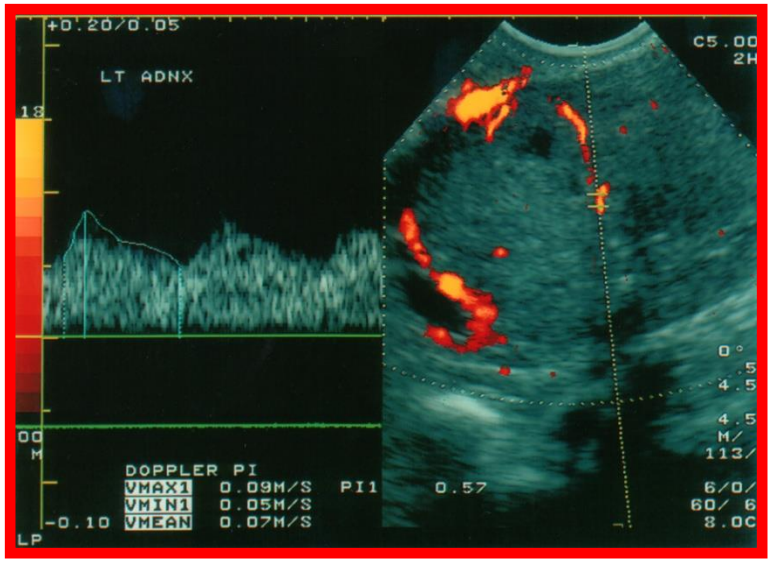
- Genetic Screening/Testing

Transvaginal Ultrasound

- Improves anatomic definition of ovaries.

- Excrescences, papillations and increased blood flow are suggestive of malignancy.





Ultrasound: Low-Risk Population

- U/S may be more effective in lower-risk populations
- Prospective study (n=37,293)
  - Ages 50 and older or 25 and older with + FHx of EOC
  - Mean F/U 5.8 years
  - Specificity 98.5%; PPV 8.9%
  - 5-Yr OS in screened patients 84.6% and 53.7% in unscreened
  - ? Difference in OS due to true mortality difference vs non-randomized nature of study
  - Findings reflect high expertise in center and may not be reproducible

Van Nagell Obstet Gynecol 2011;118:1212

Ultrasound: High-Risk Population

- High-risk patients (n=4,526), per personal, and/or FHx, or BRCA+
- Screened with U/S
- 12,709 screening scans performed
- All detected EOC cases were Stage III

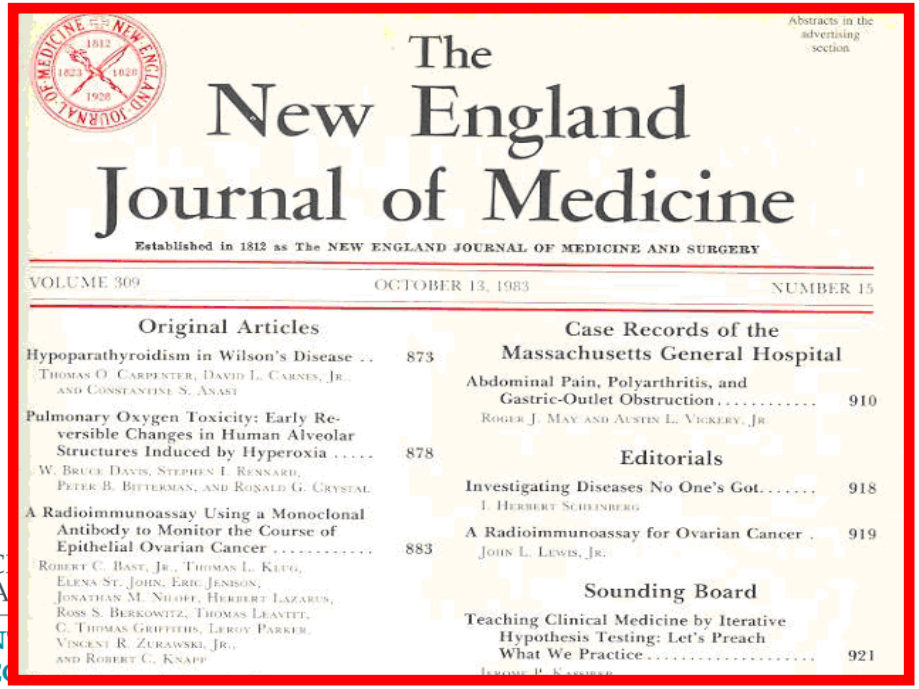
Fishman et al. Am J Obstet Gynecol 2005;192:1214

Objectives

- Early Detection Ovarian Cancer
  - Challenges
  - Ultrasound alone
  - *Combination CA 125 and Ultrasound*
- Genetic Screening/Testing

Reactivity of a Monoclonal Antibody with Human Ovarian Carcinoma

ROBERT C. BAST, JR., MARYELLEN FEENEY, HERBERT LAZARUS, LEE M. NADLER, ROBERT B. COLVIN, and ROBERT C. KNAPP, *Sidney Farber Cancer Institute, Brigham and Women's Hospital, Massachusetts General Hospital, and Harvard Medical School, Boston, Massachusetts 02115*



The New England Journal of Medicine

Established in 1812 as The NEW ENGLAND JOURNAL OF MEDICINE AND SURGERY

VOLUME 309 OCTOBER 13, 1983 NUMBER 15

Original Articles

Case Records of the Massachusetts General Hospital

Editorials

Sounding Board

% CA125 > 35U/ml According to Stage

FIGO Stage	N	% Positive
I	48/96	50.0%
II	55/61	90.0%
III	199/216	92.1%
IV	77/82	93.9%
Total	615/723	85.1%

Jacobs I, Bast R. Human Reprod 1989;4:1

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

CA 125

- Remains the single most sensitive and specific marker for ovarian cancer to date.

However…

- Ovarian Cancer Incidence in Postmenopausal Women: 1 in 2,000 women/year
  - CA125 Specificity (> 30U/ml): 98%
  - CA125 Sensitivity: 63%
  - Positive Predictive Value: 2%

- Low incidence and moderate specificity result in unacceptably low positive predictive value.

Screening Trials

Concurrent testing with CA 125 and TVUS

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

Average Risk

United Kingdom Familial Ovarian Cancer Screen Study (UK FOCSS)

High-Risk

Sequential testing (CA 125-triggered TVUS)

United Kingdom Collaborative Trial of Ovarian Cancer Screening (U.K.C.T.O.C.S.)

PLCO

- 68,557 postmenopausal women, age 55-74
- Randomized to annual screening with TVUS and CA-125 vs usual care
  - Annual CA-125 for 6 years and TVUS for 4 years
  - Management of abnormal tests results at discretion of provider

Buys SS, et al. Am J Obstet Gynecol. 2005;193:1630-9.

PLCO

- Data from baseline analysis of 28,816 women randomized to screening:
  - 1,740 abnormal CA-125 *OR* TVUS; 34 had both
  - 1/3 women with abnormal test had surgery
  - 570 women had surgery

    29 cancers found, 20 were invasive (90% of these were stage III/IV)

- CA125 ↑ in 1.5% (PPV 3.7%)

- TVS abnormal in 4.7% (PPV 1.0%)

- PPV of both tests abnormal 23.5%

Buys SS, et al. Am J Obstet Gynecol. 2005;193:1630-9.

PLCO (Final Results)

- Women Diagnosed with ovarian cancer
  - Screening group : N = 212
  - No Screening group: N = 176

- No difference in the stage between groups (77% vs. 78% advanced stage)

- No difference in mortality

- False-positive results in 3,285 and 1,080 underwent surgery
  - 15% who had false-positive finding experienced at least one serious complication

Partridge E, et al. Obstet Gynecol. 2009;113:775-782

United Kingdom Collaborative Trial of Ovarian Cancer Screening (U.K.C.T.O.C.S.)

Sequential testing has not been evaluated in high-risk individuals

MASSACHUSETTS GENERAL HOSPITAL
VINCENT OBSTETRICS & GYNECOLOGY

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Menon U, et al. Lancet Oncol. 2009;10:327-40.

MMS Arm

- Annual screening with CA 125, followed by TVUS if the CA 125 was abnormal, using an algorithmic guideline
- ROCA triaged women:
  - Normal:
    - Annual screening.
  - Intermediate:
    - Repeat CA125 concentration testing in 3 months.
  - Elevated:
    - Repeat CA125 concentration testing and TVUS as a second-line test in 6 weeks.

Menon U, et al. Lancet Oncol. 2009;10:327-40.

US Arm

- USS as the primary test.
- Normal: Annual screening.
- Unsatisfactory: Repeat in 3 months.
- Abnormal: Scan with a senior ultrasonographer within 6 weeks.
- Women with persistent abnormalities had clinical assessment and additional investigations within the NHS by a trial clinician.

Menon U, et al. Lancet Oncol. 2009;10:327-40.

U.K.C.T.O.C.S. Initial Screening Data

	Multimodal	TVUS
Total surgeries	97	845
Primary invasive cancers	34	24
Screen negative cancers in 1 yr	4	8
Surgeries per positive screen	3	35
% early Stage I/II cancers	47%	50%
Performance		
Sensitivity	89.5%	75.9%
Specificity	99.8%	98.2%
PPV	35.1%	2.8%

Menon U, et al. Lancet Oncol. 2009;10:327-40.

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

U.K.C.T.O.C.S.

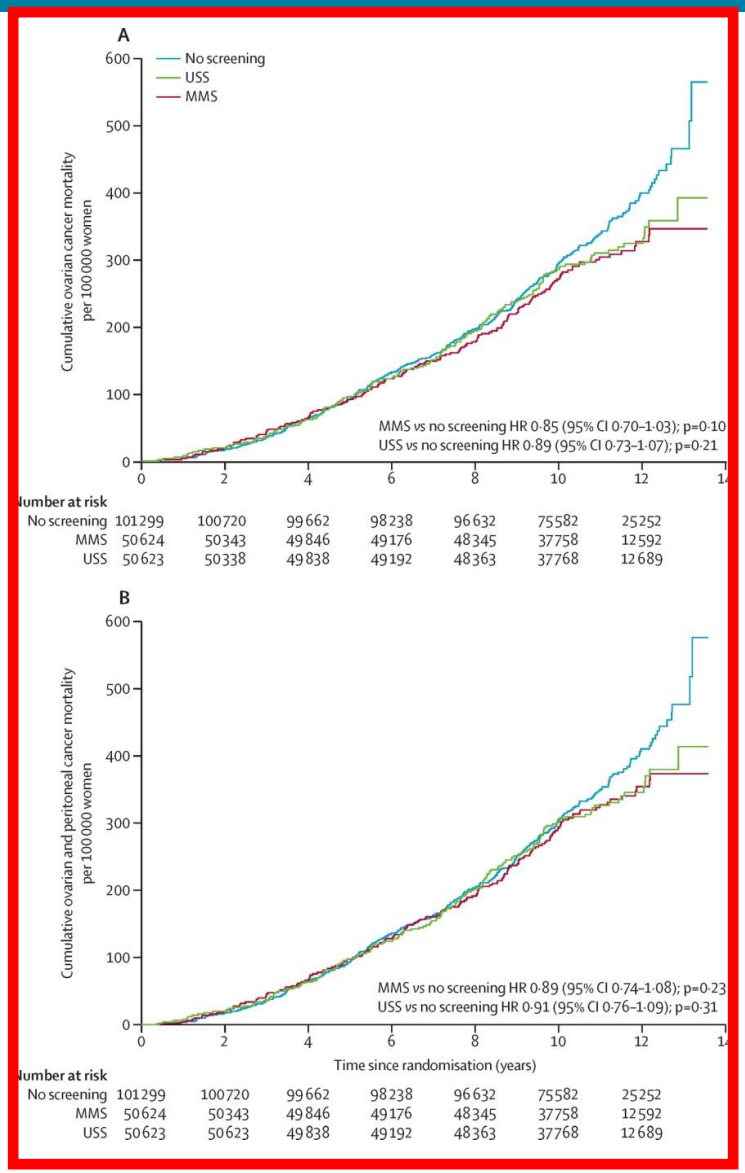
- Annual screening ended in December 2011 and follow-up lasted until 31st December 2014.
- The median follow-up was 11.1 years.
- Ovarian cancers were diagnosed in 630 (no screening), 338 (MMS), 314 (USS) women.
- Mortality reduction over years 0 -14 of 15% with MMS, and 11% with USS which were not significant.
  - MMS:
    - Years 0-7: 8% relative reduction in mortality
    - Years 8-14: 23% relative reduction in mortality
  - USS: 2% and 21%.

Jacobs I, Lancet 2016; 387: 945–56

U.K.C.T.O.C.S. (A) Cumulative ovarian cancer and (B) ovarian and peritoneal cancer deaths

A

B

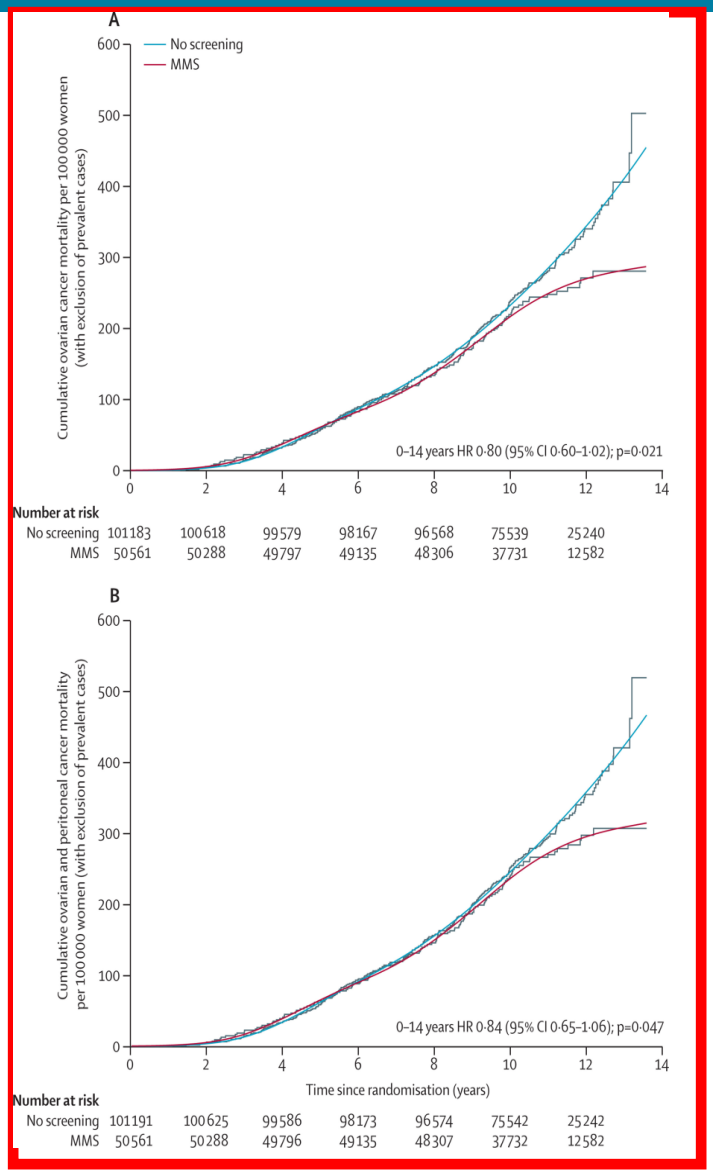


MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

U.K.C.T.O.C.S. (A) Cumulative ovarian cancer and (B) ovarian and peritoneal deaths in MMS and no screening groups after exclusion of prevalent cases

A

B



Ovarian cancer mortality *20%* *lower* in MMS group

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

U.K.C.T.O.C.S.

- The number needed to screen in the MMS group to prevent one ovarian cancer death at 14 years was 641.

Objectives

- Early Detection Ovarian Cancer
  - Challenges
  - Ultrasound alone
  - Combination CA 125 and Ultrasound
- Genetic Screening/Testing

United Kingdom Familial Ovarian Cancer Screen Study (UK FOCSS)

- Concurrent testing with CA 125 and TVUS in high-risk patients
- N=3563 women with FHx ovarian cancer syndrome, declining rrBSO
- Screened annually (mean 3.2 yrs) with TVUS and CA-125
- Sensitivity for incident OC 81-87.5%
  - Depending on whether occult OC dx at time of rrSO prior to study end
- PPV: 25.5% (exceeds 10% threshold)
- Four women underwent surgery for each cancer case

Rosenthal et al. JCO 2013;49

Other Tumor Markers

- Human epididymis protein 4 (HE4)
  - Higher sensitivity than CA 125 when comparing ovarian cancer patients with patients with benign gynecologic disease
  - Approved for monitoring patients with EOC for recurrence or progression
- Combination of biomarkers
  - Studies needed to validate this approach
- Multi-analyte blood test for genetic alterations and tumor-specific biomarkers
  - Not commercially available
  - Sensitivity (98 percent) and specificity (>99 percent) for detection of ovarian cancer at an early stage

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Screening for Ovarian Cancer
US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

JAMA | US Preventive Services Task Force | EVIDENCE REPORT

Screening for Ovarian Cancer
Updated Evidence Report and Systematic Review for the US Preventive Services Task Force

Jillian T. Henderson, PhD; Elizabeth M. Webber, MS; George F. Sawaya, MD

JAMA. 2018 Feb 13;319(6):588-594
JAMA. 2018 Feb 13;319(6):595-606

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

US Preventive Services Task Force Recommendation Statement

- USPSTF has updated its 2018 recommendations on screening for EOC
- "Recommends *against* screening for ovarian cancer in *asymptomatic* women"
- D recommendation
  - Based on rigorous evaluation of evidence of benefits and harms of screening
  - No ambiguity
  - No current strategy for early detection is recommended for women at average risk

JAMA. 2018 Feb 13;319(6):588-594
JAMA. 2018 Feb 13;319(6):595-606

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Society of Gynecologic Oncology

ACOG COMMITTEE OPINION

Number 716 • September 2017
(Reaffirmed 2019)

(Replaces Committee Opinion Number 477, March 2011)

- Currently, there is no strategy for early detection of ovarian cancer that reduces ovarian cancer mortality.

- The use of transvaginal ultrasonography and tumor markers (such as CA 125), alone or in combination, for the early detection of ovarian cancer in average-risk women have not been proved to reduce mortality, and harms exist from invasive diagnostic testing (eg, surgery) resulting from false-positive test results

Objectives

- Early Detection Ovarian Cancer
  - Challenges
  - Ultrasound alone
  - Combination CA 125 and Ultrasound

- *Genetic Screening/Testing*

Management Issues

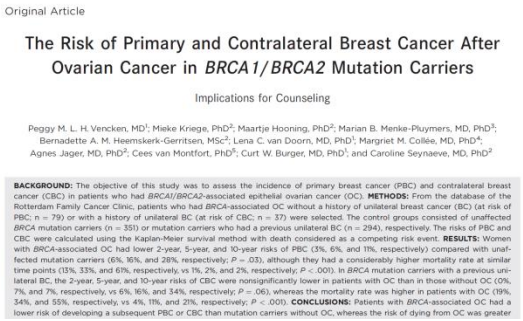
- Mutation carriers with ovarian cancer
  - BRCA
  - HNPCC

- Patients without cancer

  High risk gene mutation carriers
  - BRCA1/2
  - Lynch
  - Cowden

  New cancer predisposition genes
  - BRIP1
  - RAD51C
  - RAD51D

  Family History Only



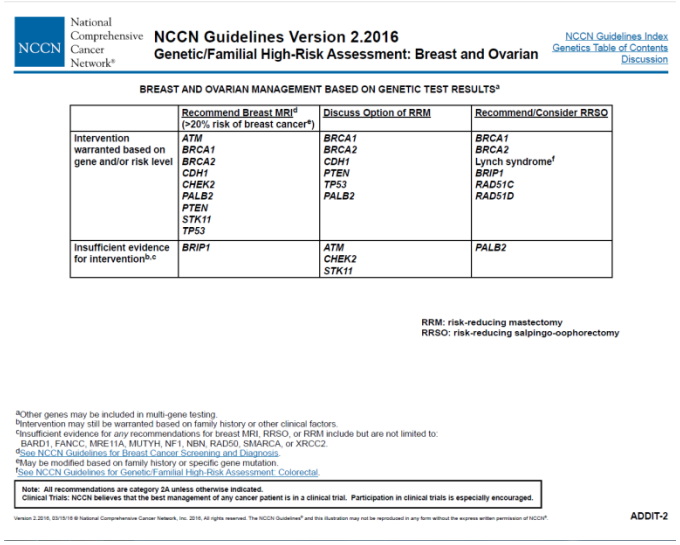
Original Article

The Risk of Primary and Contralateral Breast Cancer After Ovarian Cancer in *BRCA1/BRCA2* Mutation Carriers

Implications for Counseling

Peggy M. L. H. Vencken, MD[1]; Mieke Kriege, PhD[2]; Maartje Hooning, PhD[2]; Marian B. Menke-Pluymers, MD, PhD[3]; Bernadette A. M. Heemskerk-Gerritsen, MSc[2]; Lena C. van Doorn, MD, PhD[1]; Margriet M. Collée, MD, PhD[4]; Agnes Jager, MD, PhD[2]; Cees van Montfort, PhD[5]; Curt W. Burger, MD, PhD[1]; and Caroline Seynaeve, MD, PhD[2]

BACKGROUND: The objective of this study was to assess the incidence of primary breast cancer (PBC) and contralateral breast cancer (CBC) in patients who had *BRCA1/BRCA2*-associated epithelial ovarian cancer (OC). **METHODS:** From the database of the Rotterdam Family Cancer Clinic, patients who had *BRCA*-associated OC without a history of unilateral breast cancer (BC) (at risk of PBC; n = 79) or with a history of unilateral BC (at risk of CBC; n = 37) were selected. The control groups consisted of unaffected *BRCA* mutation carriers (n = 351) or mutation carriers who had a previous unilateral BC (n = 294), respectively. The risks of PBC and CBC were calculated using the Kaplan-Meier survival method with death considered as a competing risk event. **RESULTS:** Women with *BRCA*-associated OC had lower 2-year, 5-year, and 10-year risks of PBC (3%, 6%, and 11%, respectively) compared with unaffected mutation carriers (6%, 16%, and 28%, respectively; *P* = .03), although they had a considerably higher mortality rate at similar time points (13%, 33%, and 61%, respectively, vs 1%, 2%, and 2%, respectively; *P* < .001). In *BRCA* mutation carriers with a previous unilateral BC, the 2-year, 5-year, and 10-year risks of CBC were nonsignificantly lower in patients with OC than in those without OC (0%, 7%, and 7%, respectively, vs 6%, 16%, and 34%, respectively; *P* = .06), whereas the mortality rate was higher in patients with OC (19%, 34%, and 55%, respectively, vs 4%, 11%, and 21%, respectively; *P* < .001). **CONCLUSIONS:** Patients with *BRCA*-associated OC had a lower risk of developing a subsequent PBC or CBC than mutation carriers without OC, whereas the risk of dying from OC was greater



NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Genetic/Familial High-Risk Assessment: Breast and Ovarian

NCCN Guidelines Index
Genetics Table of Contents
Discussion

BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS[a]

	Recommend Breast MRI[d] (>20% risk of breast cancer[e])	Discuss Option of RRM	Recommend/Consider RRSO
Intervention warranted based on gene and/or risk level	*ATM* *BRCA1* *BRCA2* *CDH1* *CHEK2* *PALB2* *PTEN* *STK11* *TP53*	*BRCA1* *BRCA2* *CDH1* *PTEN* *TP53* *PALB2*	*BRCA1* *BRCA2* Lynch syndrome[f] *BRIP1* *RAD51C* *RAD51D*
Insufficient evidence for intervention[b,c]	*BRIP1*	*ATM* *CHEK2* *STK11*	*PALB2*

RRM: risk-reducing mastectomy
RRSO: risk-reducing salpingo-oophorectomy

[a]Other genes may be included in multi-gene testing.
[b]Intervention may still be warranted based on family history or other clinical factors.
[c]Insufficient evidence for *any* recommendations for breast MRI, RRSO, or RRM include but are not limited to: BARD1, FANCC, MRE11A, MUTYH, NF1, NBN, RAD50, SMARCA, or XRCC2.
[d]See NCCN Guidelines for Breast Cancer Screening and Diagnosis.
[e]May be modified based on family history or specific gene mutation.
[f]See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

ADDIT-2

MGH 1811 MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Germline Mutation Profile Among Hispanic Women with EOC

- 1,186 Hispanic women
- All women with a personal history of EOC from the U.S. and Latin America (Latin America, Mexico, Colombia, and Peru), enrolled in the Clinical Cancer Genomics Community Research Network registry
- Assessed prevalence of pathogenic variants in BRCA 1 and 2 and other genes
- Contrasted mutation profile between Hispanics in Latin America, US Hispanics, Ashkenazi Jewish in the US, and other US non-Hispanics
- Similar to rate for Ashkenazi Jewish population

Chavarri, Y, et al. ASCO Abstract 1584

Results
N=1,186; 262 (22%) had PV in BRCA genes

Background	# in Study	BRCA Mutation Frequency	p-value	BRCA Negative Other PV
Latin America	209	30.6%	0.14	2.9%
US Hispanic	254	29.9%		
Ashkenazi Jewish	78	38.4%		3.8%
Other Non-Hispanic	645	14.3%	0.03	4.0%

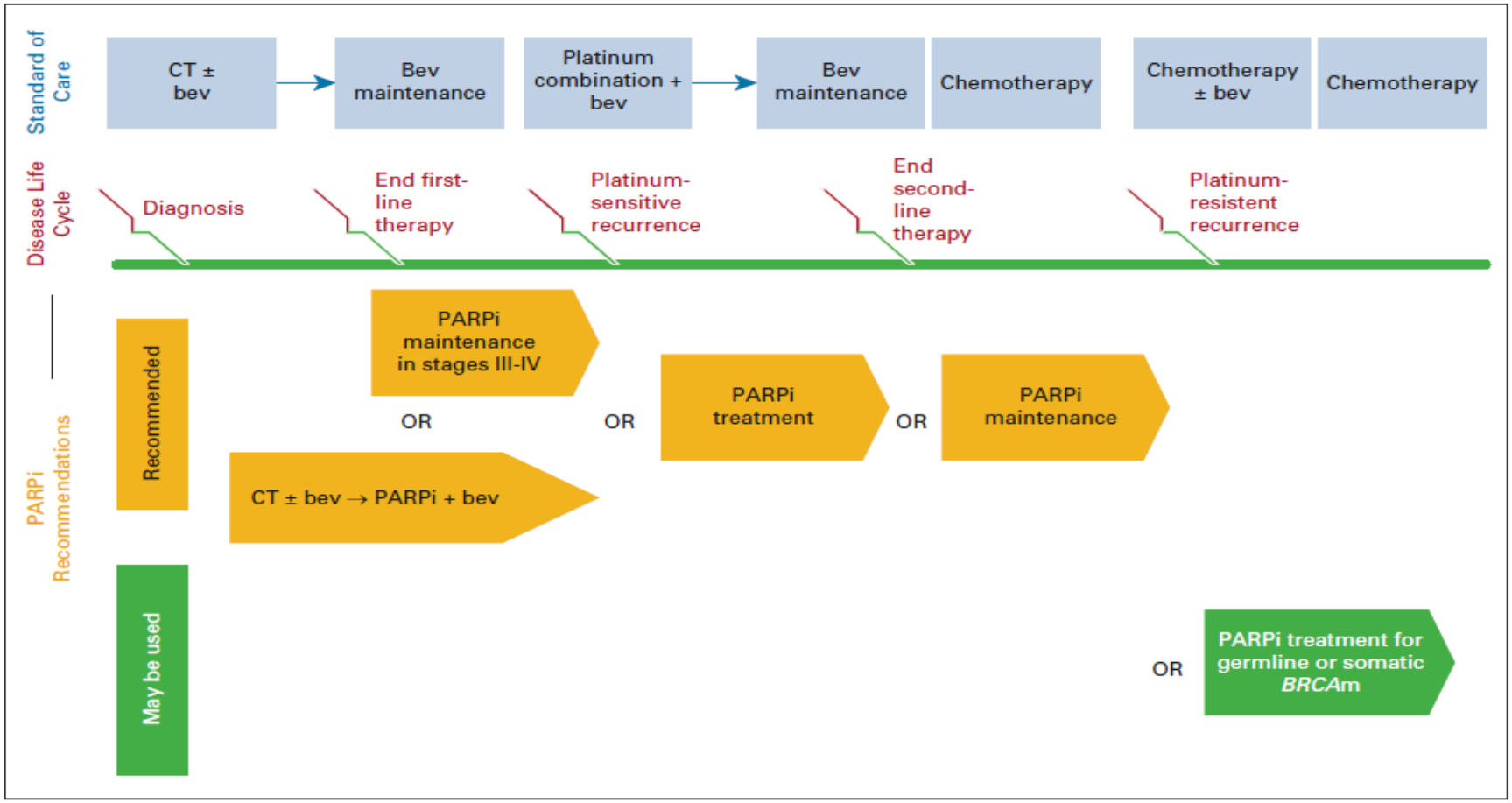
Hispanics with EOC have elevated frequency of PV BRCA mutation, similar to AJ and significantly higher than non-Hispanics

Chavarri, Y, et al. ASCO Abstract 1584

MASSACHUSETTS GENERAL HOSPITAL
VINCENT OBSTETRICS & GYNECOLOGY

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Randomized Controlled Trials of PARP Inhibitor Maintenance



Tew et al. JCP 2021;38:3468-93

MASSACHUSETTS GENERAL HOSPITAL
CANCER CENTER

Key Criteria for Hereditary Cancer Risk Evaluation and Possible Testing

- Patients with:
  - Female breast cancer diagnosed ≤ 45-50 years
  - Triple-negative breast cancer (TNBC) diagnosed ≤ 60 years
  - Two or more primary breast cancers
  - Invasive ovarian or fallopian tube cancer, or primary peritoneal cancer
  - Male breast cancer
  - Metastatic prostate cancer or exocrine pancreatic cancer
  - Any HBOC-associated cancers, regardless of age at diagnosis, and of Ashkenazi (central or eastern European) Jewish ancestry

Breast and Ovarian Management Based on Genetic Testing Results

	Recommend Breast MRI (>20% risk of breast cancer)	Discuss option of RRM	Recommend/ Consider RRSO
Intervention warranted based on gene and/or risk level	ATM BRCA1 BRCA2 CDH1 CHEK2 PALB2 PTEN STK11 TP53	BRCA1 BRCA2 CDH1 PTEN PALB2 TP53	BRCA1 BRCA2 Lynch Syndrome BRIP1 RAD51C RAD51D
Insufficient evidence for intervention	BRIP1		PALB2

Screening Hereditary Ovarian Cancer Syndromes: Summary

- Routine screening in general population not recommended
  - USPSTF, SGO, ACOG, Canadian Task Force on Periodic Health Examination
- Women with identified hereditary ovarian cancer syndromes (NCCN, SGO)
  - TV U/S and CA-125 every 6 months
  - Start at age 30-35 or 5-10 yrs earlier than earliest age of 1st dx of EOC in family
- ACOG
  - No evidence that screening improves survival in high-risk patients
- NCI
  - Insufficient evidence to support screening in *any* population

Hereditary Ovarian Cancer Syndromes: Risk-Reducing Surgery

- Risk-reducing salpingo-oophorectomy (RRSO)
  - Between ages 35-40 or upon completion of childbearing
  - Ovarian cancer onset in BRCA2 mutations occurs 8-10 years later than in BRCA1 carriers
  - In premenopausal women, oophorectomy reduces risk of breast cancer by up to 50% depending upon age of procedure
  - May delay RRSO in BRCA2 mutation carriers until age 40-45 if patient has maximized breast cancer prevention (i.e. s/p mastectomy)
- Salpingectomy alone is not standard of care for risk reduction

Conclusions

- Screening for EOC starts with family history and identification of high-risk vs average-risk women
- “Screening” options have included CA-125, ultrasound
- No evidence to support a benefit from ovarian cancer screening in average-risk women
- No screening strategy has demonstrated reduction in mortality
- All screening strategies associated with high rate of false-positive tests and risk of harm from invasive testing
- For high-risk women, rrBSO is standard of care
  - “Screening” with CA-125 and TV U/S every 6 months
  - Starting at age 30 or 5-10 years before the earliest age of 1st dx of EOC in the family
  - Lack of high-quality data to inform these recommendations

Thank you