Rebooting Ovarian Cancer

John O Schorge, MD, FACS


WHAT WE KNOW

OVARIAN CANCER

survival rates

	Invasive epithelial ovarian cancer	Ovarian stromal tumors	Ovarian germ cell tumors	Fallopian tube carcinoma
Stage 1	90%	95%	98%	87%
Stage 2	70%	78%	94%	86%
Stage 3	39%	65%	87%	52%
Stage 4	17%	35%	69%	40%

Source: https://www.cancer.org/cancer/ovarian-cancer/detection-diagnosis-staging/survival-rates.html healthline

KNOW THE SYMPTOMS

BLOATING

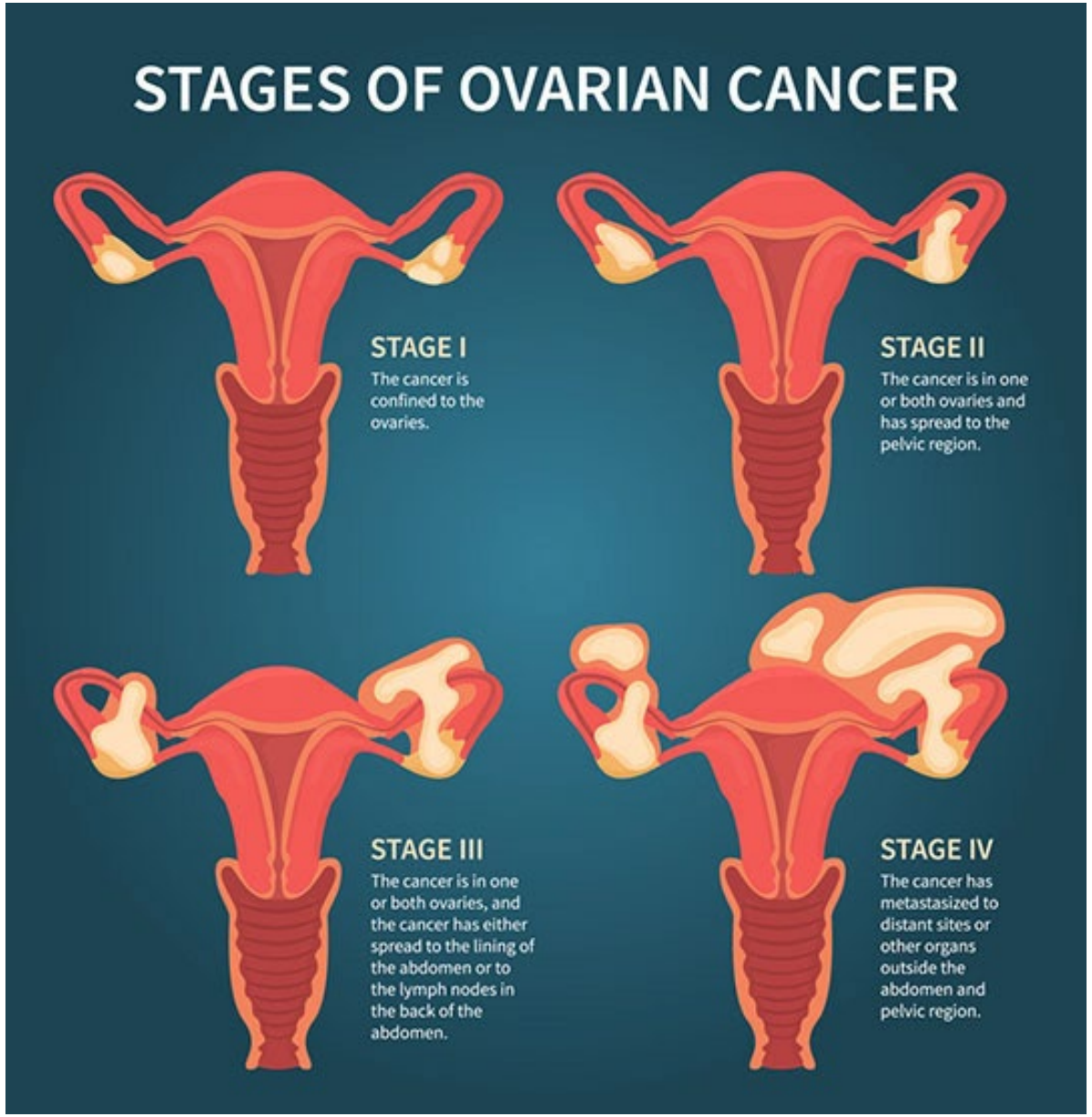
DIFFICULTY EATING

PELVIC / ABDOMINAL PAIN

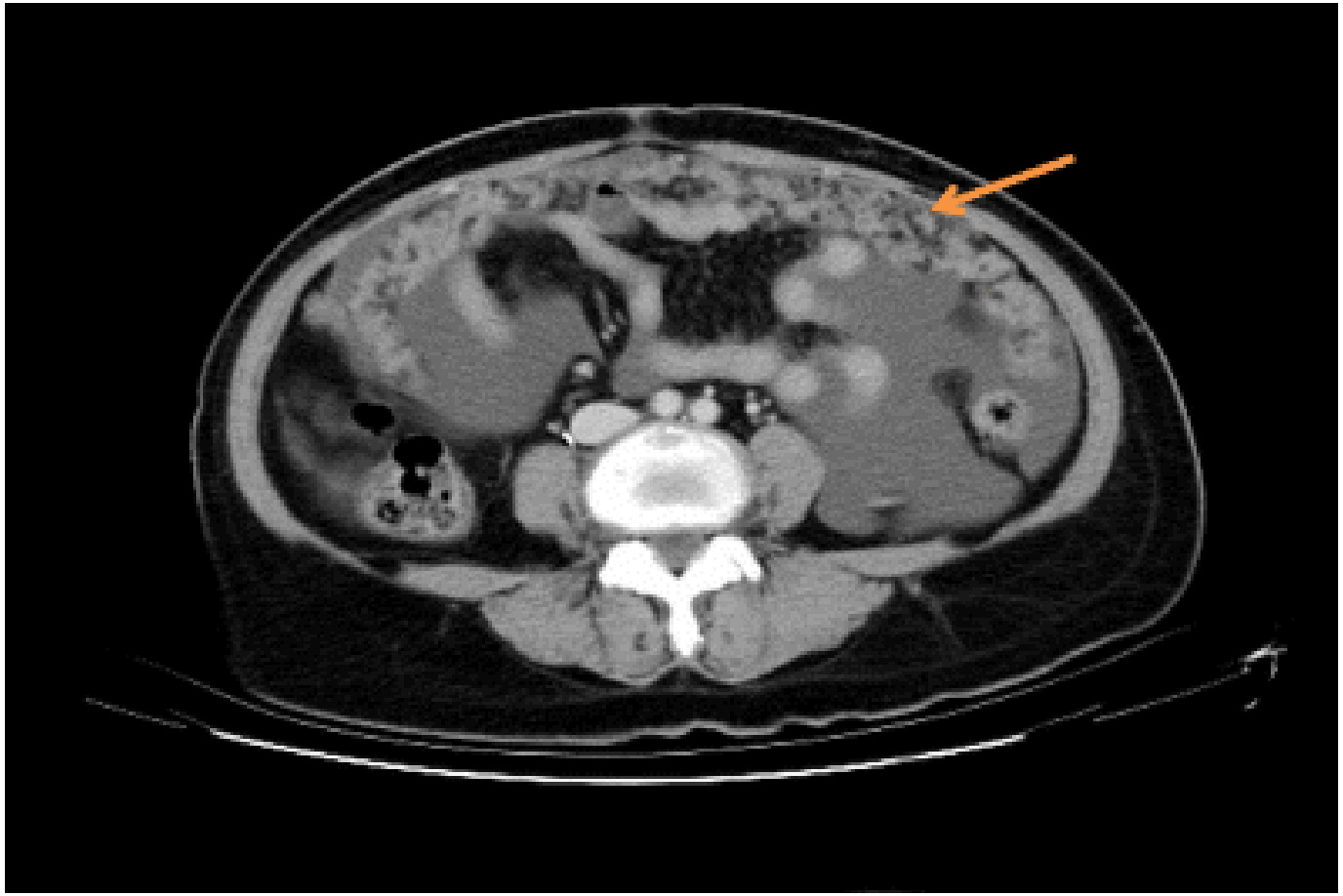
URINARY FREQUENCY

If these symptoms occur for **MORE THAN 2 WEEKS** and these symptoms are new or unusual for you, see a gynecologist and ask about ovarian cancer. Research shows that seeing a gynecologic oncologist for surgery and treatment significantly improves outcomes.

- 50ish year old
- Delayed diagnosis


STAGES OF OVARIAN CANCER
STAGE I
The cancer is confined to the ovaries.
STAGE II
The cancer is in one or both ovaries and has spread to the pelvic region.
STAGE III
The cancer is in one or both ovaries, and the cancer has either spread to the lining of the abdomen or to the lymph nodes in the back of the abdomen.
STAGE IV
The cancer has metastasized to distant sites or other organs outside the abdomen and pelvic region.

Two-thirds still have stage III/IV EOC at dx



Residual Disease Status and Survival in Advanced Ovarian Cancer

Author [Ref.]	Year	Median survival (months)	
		Optimal[a]	Suboptimal
Hacker *et al.* [24]	1983	18	6
Vogl *et al.* [37]	1983	40	16
Delgado *et al.* [38]	1984	45	16
Pohl *et al.* [30]	1984	45	16
Conte *et al.* [40]	1985	25	14
Posada *et al.* [41]	1985	30	18
Chen and Bochner [10]	1985	21	8
Louie *et al.* [43]	1986	24	15
Redman *et al.* [44]	1986	37	26
Neijt *et al.* [45]	1987	40	21
Hainsworth *et al.* [46]	1988	72	13
Piver *et al.* [47]	1988	48	21
Sutton *et al.* [42]	1989	45	23
Bertelson [20]	1990	50	18
Eisenkop *et al.* [21]	1992	31	18
Michel *et al.* [2]	1996	24	14

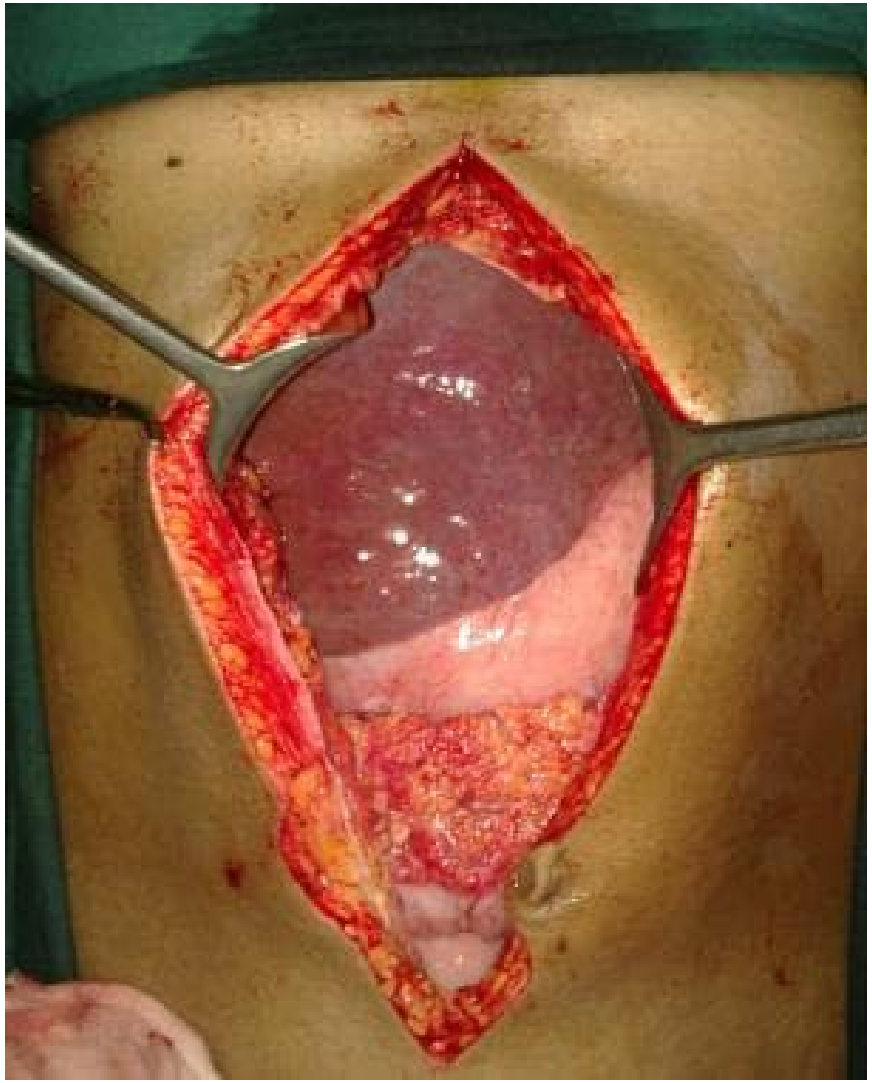
[a] Defined as <1 or <2 cm.

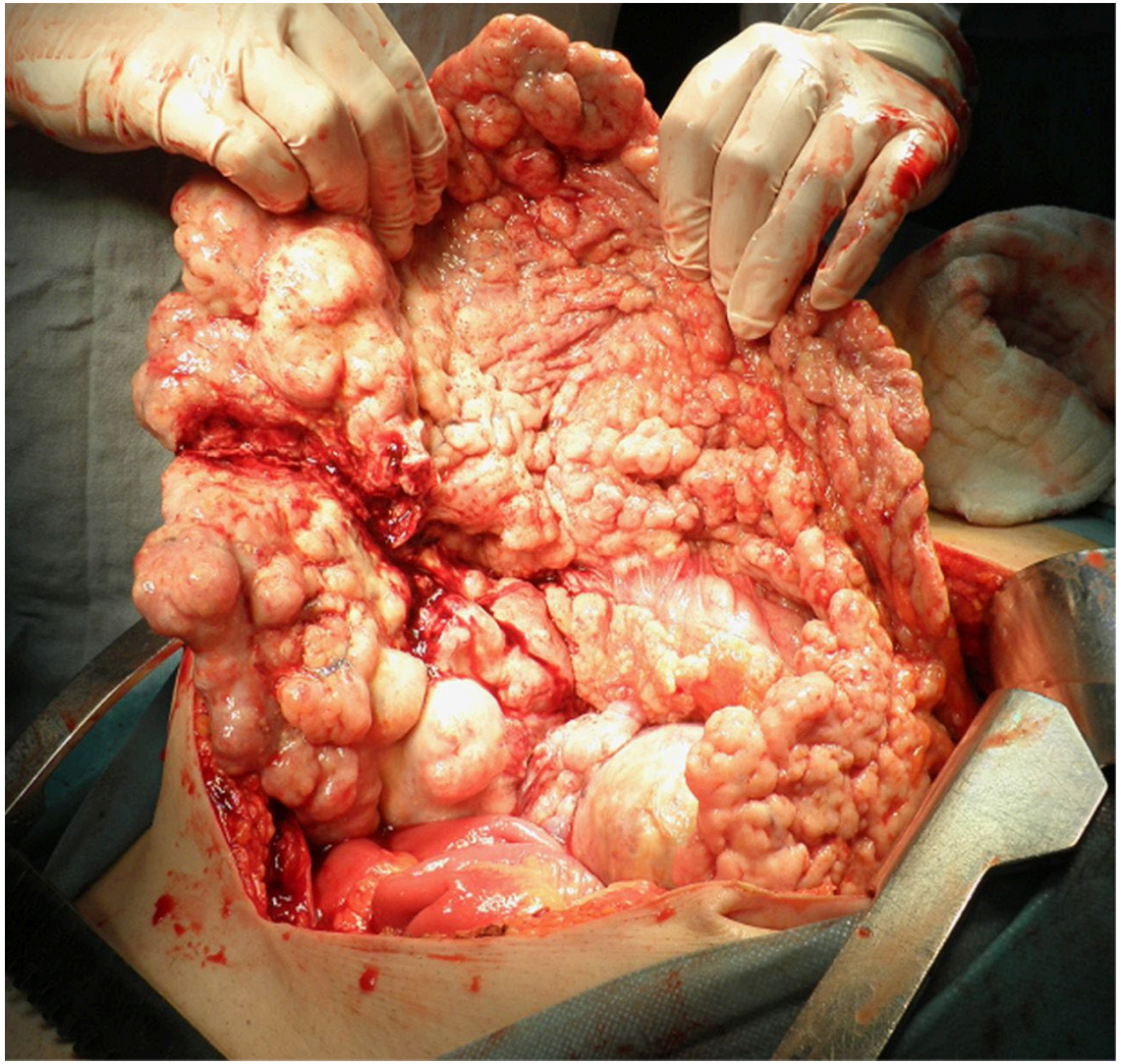
Incidence of Optimal Cytoreduction in Advanced Ovarian Cancer[a]

Author [Ref.]	Year	*N*	% Optimal[b]
Smith and Day [48]	1979	792	24
Wharton and Edwards [50]	1983	395	39
Neijt *et al.* [49]	1984	186	31
Neijt *et al.* [45]	1987	191	49
Bertelson [20]	1990	349	26
Eisenkop *et al.* [21]	1992	263	54
Venesmaa *et al.* [11]	1992	264	36
Kehoe *et al.* [29]	1994	811	35
LoCoco *et al.* [28]	1995	167	23

[a] Only studies with over 100 patients are included.
[b] Defined as <1 or <2 cm.

The preponderance of retrospective single-institution reports throughout the 1980s and 90s essentially solidified laparotomy with attempted primary debulking as the de facto standard of care, despite lackluster rates of achieving an “optimal” result





- Serous tumors frequently had a “peritoneum that was completely studded with implantations”
- “surgical removal is certainly extremely important”
- Effects of x-ray treatment are ‘mixed”
- “The outlook for patients with this disease is hopeless”

- 50ish year old
- Delayed diagnosis
- Vertical laparotomy
- Left disease behind
- Postop complications

The New England
Journal of Medicine

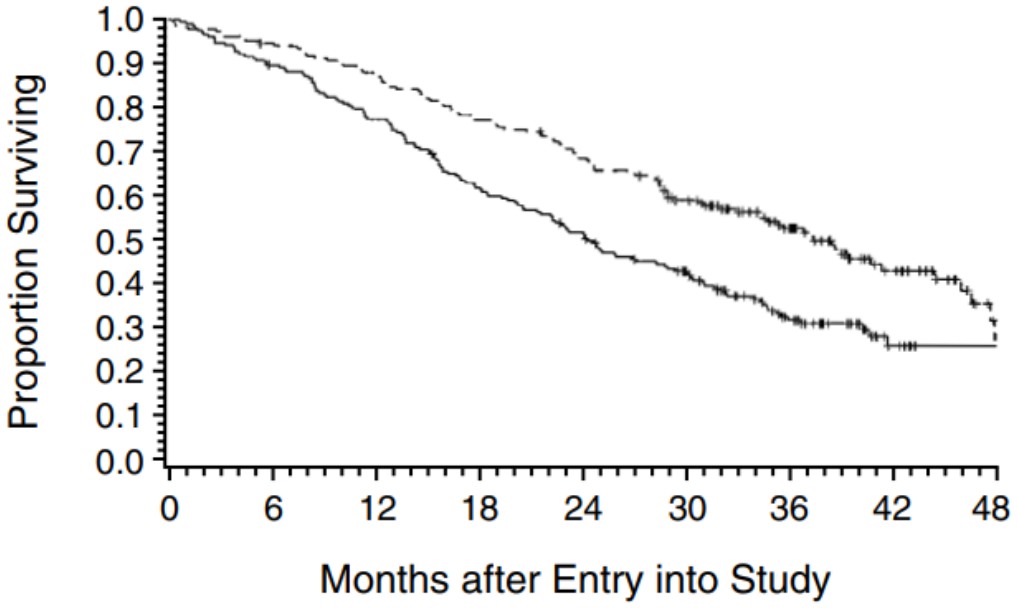
Volume 334 JANUARY 4, 1996 Number 1

CYCLOPHOSPHAMIDE AND CISPLATIN COMPARED WITH PACLITAXEL AND CISPLATIN IN PATIENTS WITH STAGE III AND STAGE IV OVARIAN CANCER

WILLIAM P. MCGUIRE, M.D., WILLIAM J. HOSKINS, M.D., MARK F. BRADY, B.S., PAUL R. KUCERA, M.D., EDWARD E. PARTRIDGE, M.D., KATHERINE Y. LOOK, M.D., DANIEL L. CLARKE-PEARSON, M.D., AND MARTIN DAVIDSON, M.D.

Abstract *Background.* Chemotherapy combinations that include an alkylating agent and a platinum coordination complex have high response rates in women with advanced ovarian cancer. Such combinations provide long-term control of disease in few patients, however. We compared two combinations, cisplatin and cyclophosphamide

in the cisplatin–paclitaxel group. Among 216 women with measurable disease, 73 percent in the cisplatin–paclitaxel group responded to therapy, as compared with 60 percent in the cisplatin–cyclophosphamide group ($P=0.01$). The frequency of surgically verified complete response was similar in the two groups. Progression-free survival was



Treatment	No. Alive	No. Dead	Total	Median Survival (mo)
—— Cisplatin + cyclophosphamide	65	137	202	24
- - - - Cisplatin + paclitaxel	86	98	184	38

Figure 2. Survival According to Treatment Group.

- Suboptimal stage III/IV
- Postop chemo
- Cisplatin 75 mg/m2
- Paclitaxel 135 mg/m2

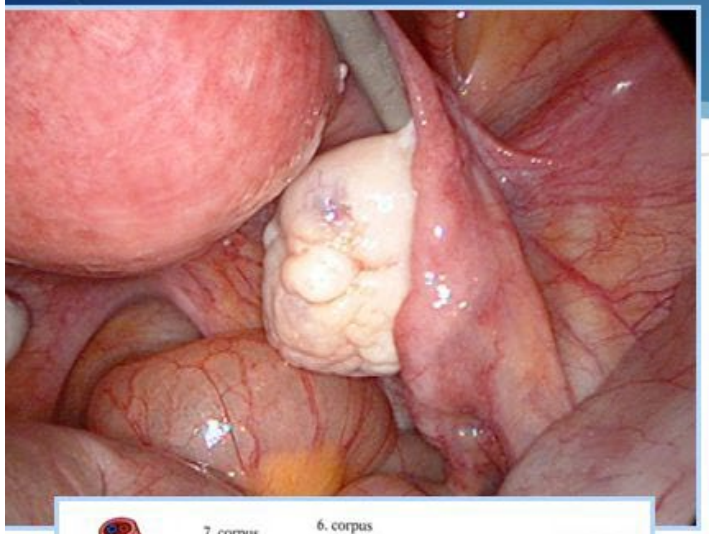
- 50ish year old
- Delayed diagnosis
- Vertical laparotomy
- Left disease behind
- Postop complications
- Resistant to carbo/pac
- Died within months

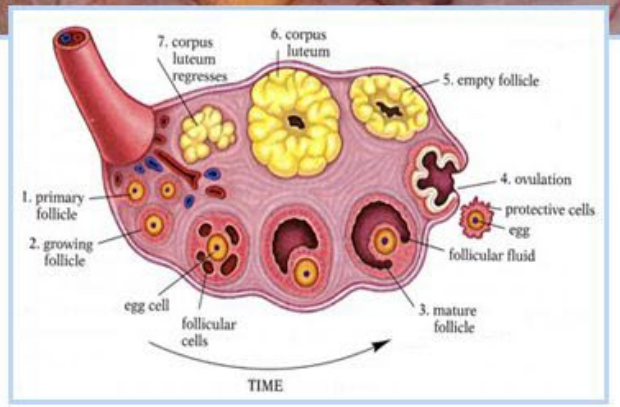

REBOOT

Educational objectives

1. An expanded knowledge base of why ovarian cancer is gradually decreasing year after year.
2. Appreciate the inability to effectively screen while being aware of early detection strategies.
3. Describe innovations in treatment that have led to dramatic improvements and unheard of cures.
4. Explore future paradigms of care and cutting-edge research to further improve outcomes.

Types of Ovarian Cancer



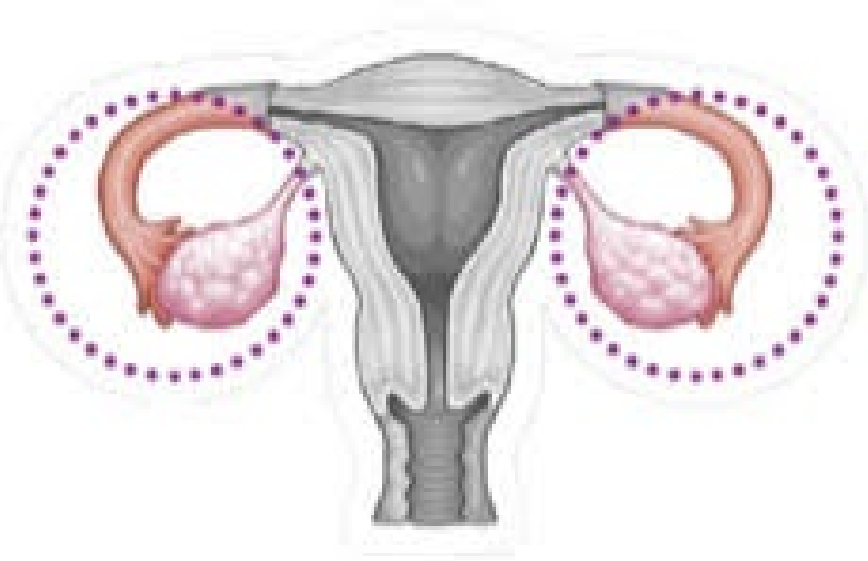


1. Epithelial Ovarian Cancer (90%)
   - Serous/Papillary serous (80%)
   - Mucinous (10%)
   - Endometrioid (10%)
   - Clear Cell
   - Brenner Tumors
   - *Borderline Tumors*
2. Germ Cell Tumors
   - Dysgerminoma
   - Yolk Sac Tumors/Endodermal sinus tumor
   - Embryonal Carcinoma
   - Choriocarcinoma
   - Teratomas
3. Sex-cord Stromal Tumors
   - Granulosa Cell Tumors
   - Fibrosarcoma
   - Sertoli-Leydig Tumors


Have you heard
of **BRCA gene**
mutations?

Have you heard of **BRCA gene mutations**?

Laparoscopic RRSO



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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Primary Fallopian Tube Malignancies in *BRCA*-Positive Women Undergoing Surgery for Ovarian Cancer Risk Reduction

Michael J. Callahan, Christopher P. Crum, Fabiola Medeiros, David W. Kindelberger, Julia A. Elvin, Judy E. Garber, Colleen M. Feltmate, Ross S. Berkowitz, and Michael G. Muto

From the Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, and Division of Women's and Perinatal Pathology, Department of Pathology Brigham and Women's Hospital; and Cancer Risk and Prevention Program, Dana-Farber Cancer Institute, Boston, MA.

Submitted April 22, 2007; accepted June 13, 2007.

Presented in part at the New England Association of Gynecologic Oncologists 25th Annual Meeting, June 2-5, 2005, Bretton Woods, NH, and the Society of Gynecologic Oncologists 37th Annual Meeting, March 22-26, 2006, Palm Springs, CA.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/07/2525-3985/$20.00

DOI: 10.1200/JCO.2007.12.2622

A B S T R A C T

Purpose
To review the frequency and location of malignancies detected after prophylactic salpingo-oophorectomy in women with *BRCA* mutations.

Methods
Medical records and pathology findings were reviewed from *BRCA*-positive women undergoing prophylactic surgery for ovarian cancer risk reduction who underwent complete examination of the adnexa. Patients undergoing this procedure between January 1999 and January 2007 were identified.

Results
From January 1999 to January 2007, 122 *BRCA*-positive patients underwent prophylactic surgery in the Division of Gynecologic Oncology at Brigham and Women's Hospital. The median age was 46.5 years (range, 33 to 76 years). Seven (5.7%) were found to have an early malignancy in the upper genital tract and all patients were age ≥ 44 years at diagnosis. Of seven consecutive cancers culled between January 1999 and January 2007, all (100%) originated in the fimbrial or ampullary region of the tube; six had an early (intraepithelial) component. Two were associated with surface implants on the ovary and two required repeated sectioning to detect microscopic carcinomas in the fimbria.

Conclusion
The distal fallopian tube seems to be the dominant site of origin for early malignancies detected in approximately 6% of women undergoing ovarian cancer risk-reduction surgery. The greatest proportion of serous cancer risk in *BRCA* mutation–positive women should be assigned to the fimbria rather than the ovary, and future clinical and research protocols should employ thorough examination of the fimbria, including multiple sections from each tissue block, to maximize detection of early malignancies in this population.

J Clin Oncol 25:3985-3990. © 2007 by American Society of Clinical Oncology

"The distal fallopian tube seems to be the site of origin for early malignancies detected in ***5%*** of women undergoing RRSO."

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Volume 5, Number 1: 35-44

http://www.clinmedres.org

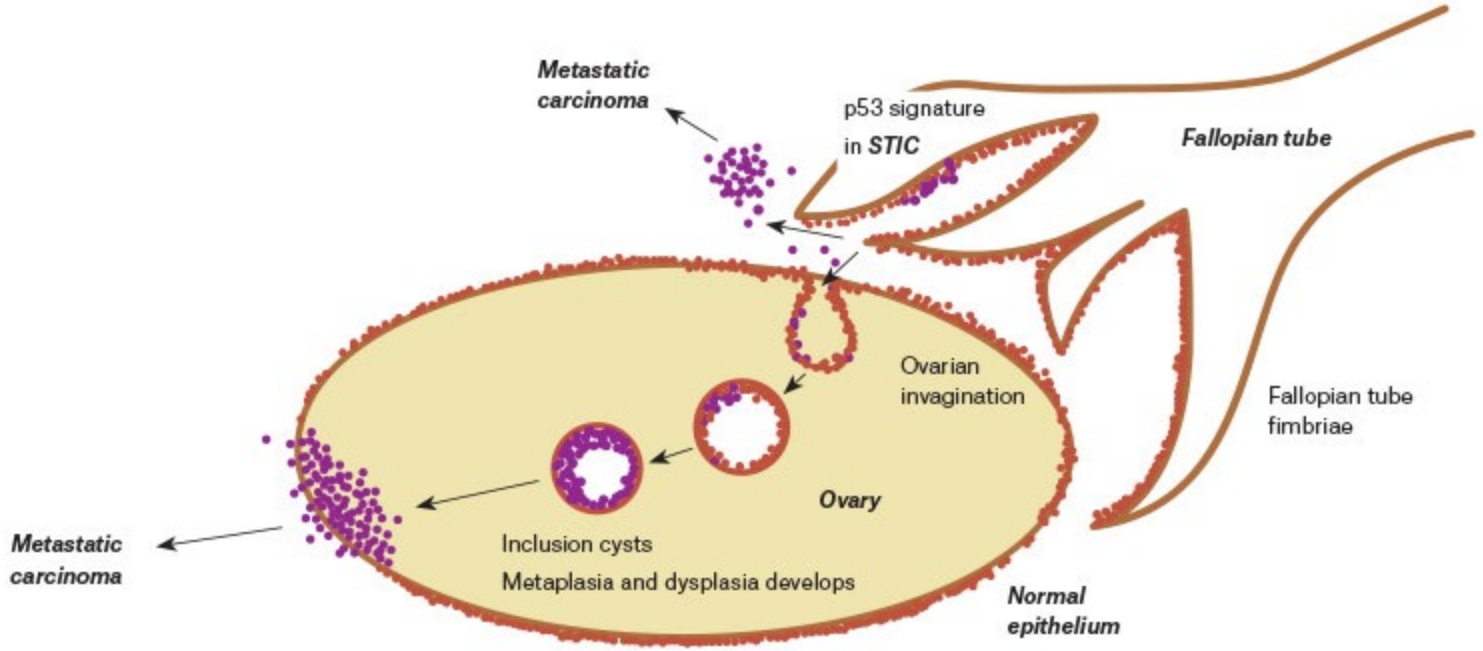
Review

Lessons from BRCA: The Tubal Fimbria Emerges as an Origin for Pelvic Serous Cancer

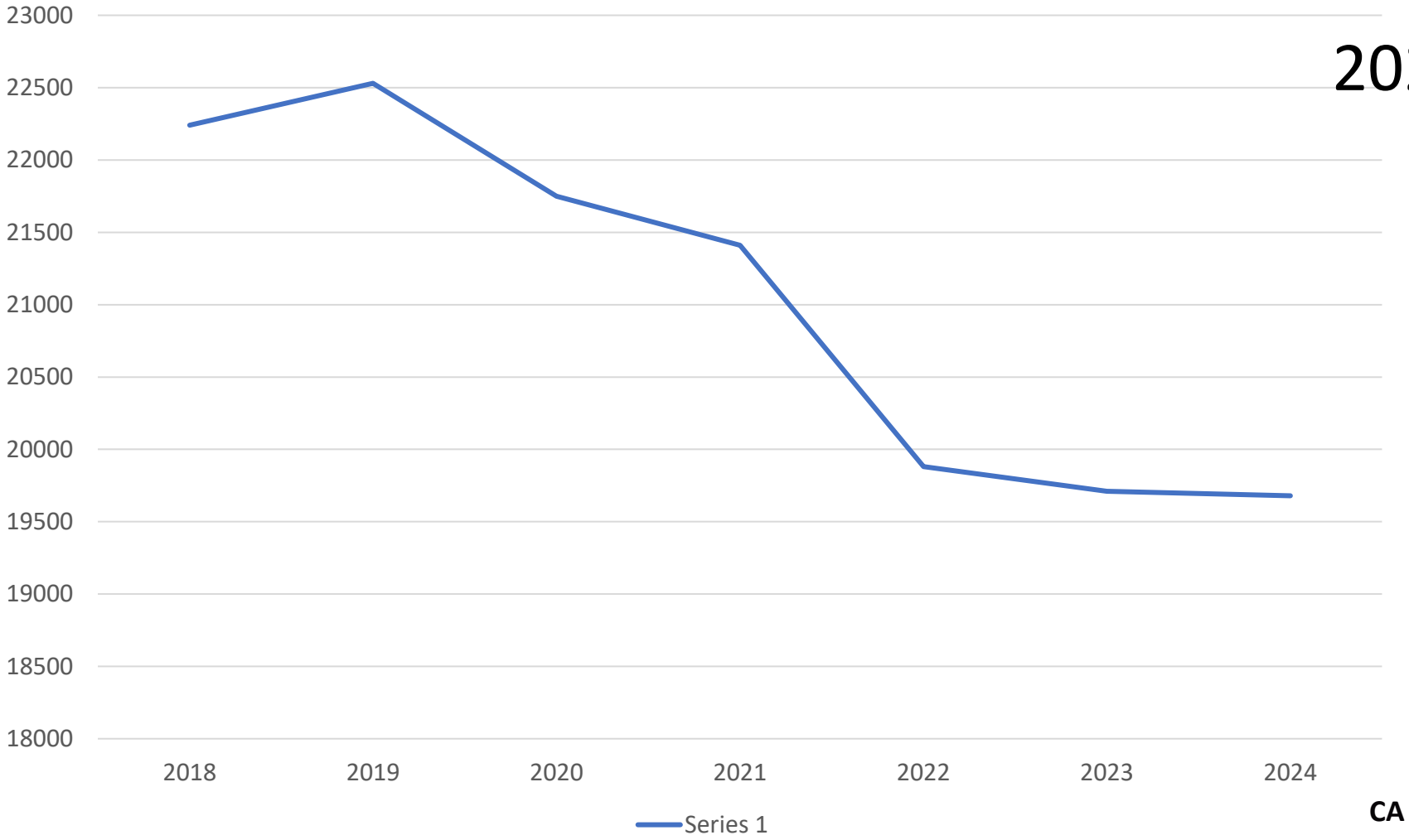
Christopher P. Crum, MD; Ronny Drapkin, MD, PhD; David Kindelberger, MD; Fabiola Medeiros, MD; Alexander Miron, PhD; and Yonghee Lee, MD

Ovarian epithelial cancer is diagnosed in approximately 25,000 women yearly in the United States, accounting for approximately 12,500 deaths. Of these tumors, serous cancer is the most lethal, due to its capacity to spread beyond the reproductive tract and involve the peritoneal surfaces or distant organs. Conventional classification systems designate tumor origins principally on the location of the largest tumor. However, despite the fact that the largest tumors typically involve the ovaries, demonstrations of a precise starting point for these tumors, including precursor lesions, have been inconsistent. In recent years, a major effort to prevent serous cancer in genetically susceptible women with mutations in BRCA1 or BRCA2 has spawned the practice of prophylactic salpingo-oophorectomy. This practice has surprisingly revealed that many early cancers in these women arise in the fallopian tube, and further studies have pinpointed the distal (fimbrial) portion as the most common site of origin. Emerging studies that carefully examine the fallopian tubes suggest a high frequency of early cancer in the fimbria in unselected women with ovarian and peritoneal serous carcinoma, raising the distinct

The path to pap serous EOC



Incidence of ovarian cancer in the USA



2024: 19,680

Decreased by 15% over past 5 years

CA Cancer J Clin 2015-2024

Does Anything Prevent Ovarian Cancer?

- Oral contraceptives
- Pregnancies
- Breast feeding (long duration)
- Tubal ligation
- Oophorectomy and hysterectomy


THING
1

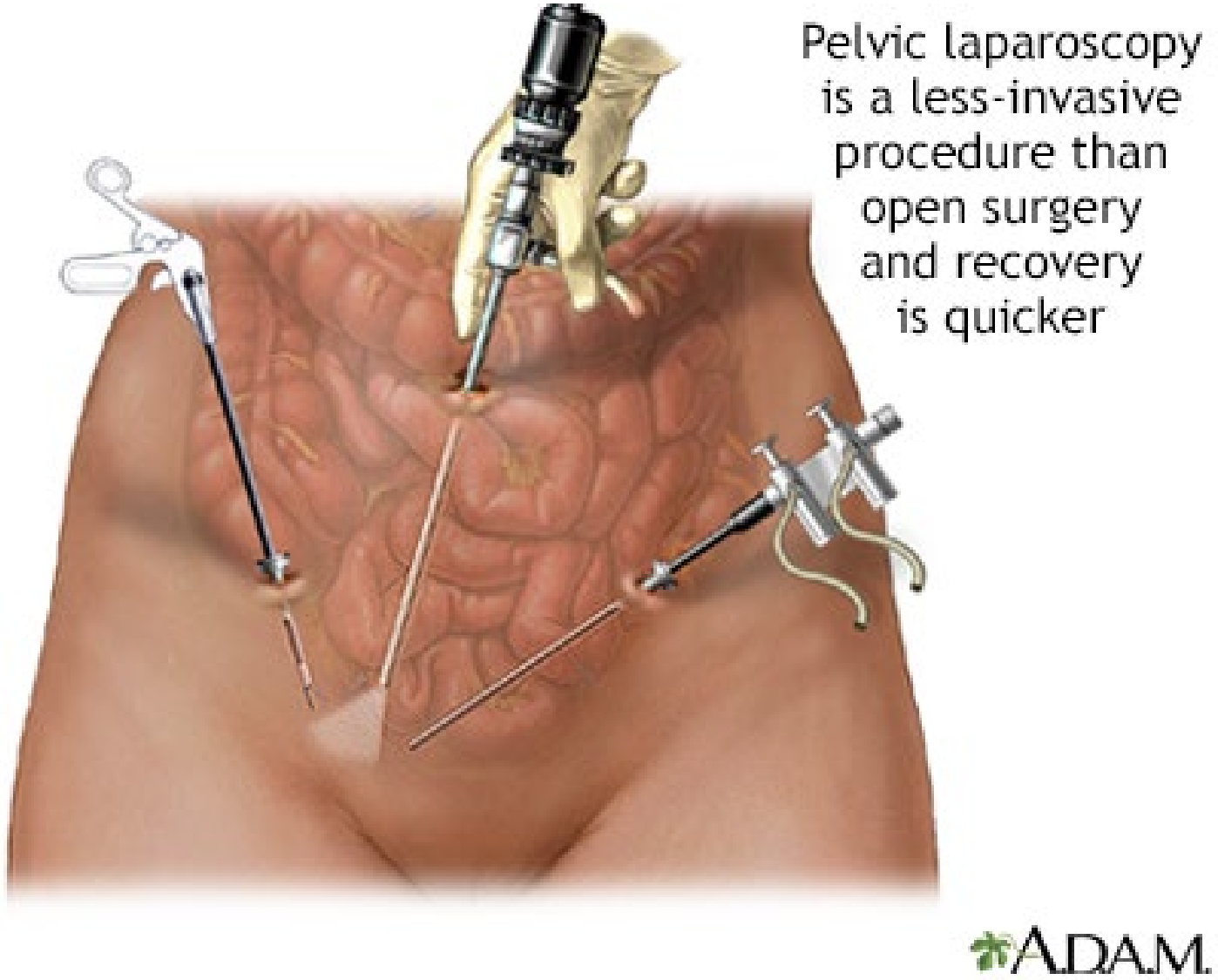
Hereditary Breast and Ovarian Cancer Multi-Gene Panel

Type of Cancer	Genes						
	ATM	BARD1	BRCA1 or BRCA2	BRIP1	CHEK2	PALB2	RAD51C or RAD51D
Breast	Yes	Yes	Yes		Yes	Yes	Maybe
Ovarian	Maybe		Yes	Yes		Maybe	Yes
Pancreatic	Yes		Yes			Yes	
Prostate	Maybe		Yes				
Colorectal (colon and rectal)					Maybe		

Key

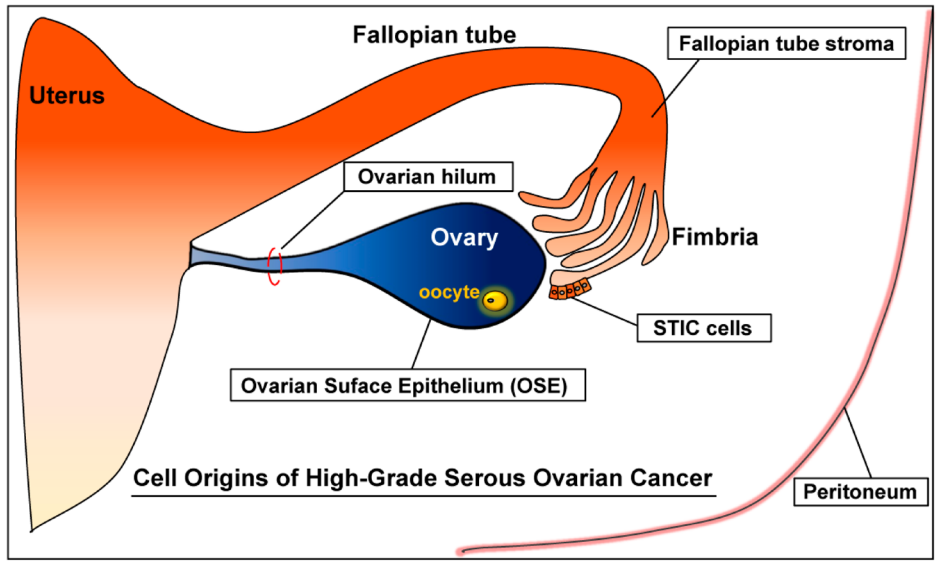
Yes: A mutation in this gene increases the risk for that type of cancer.

Maybe: A mutation in this gene may increase the risk for that type of cancer, but more research is needed.



- Laparoscopy
- Pelvic washings
- Omental biopsy
- BSO + thin sections


THING
2



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

ACOG COMMITTEE OPINION SUMMARY

Number 774

(Replaces Committee Opinion Number 620, January 2015)

For a comprehensive overview of these recommendations, the full-text version of this Committee Opinion is available at http://dx.doi.org/10.1097/AOG.0000000000003164.

Scan this QR code with your smartphone to view the full-text version of this Committee Opinion.

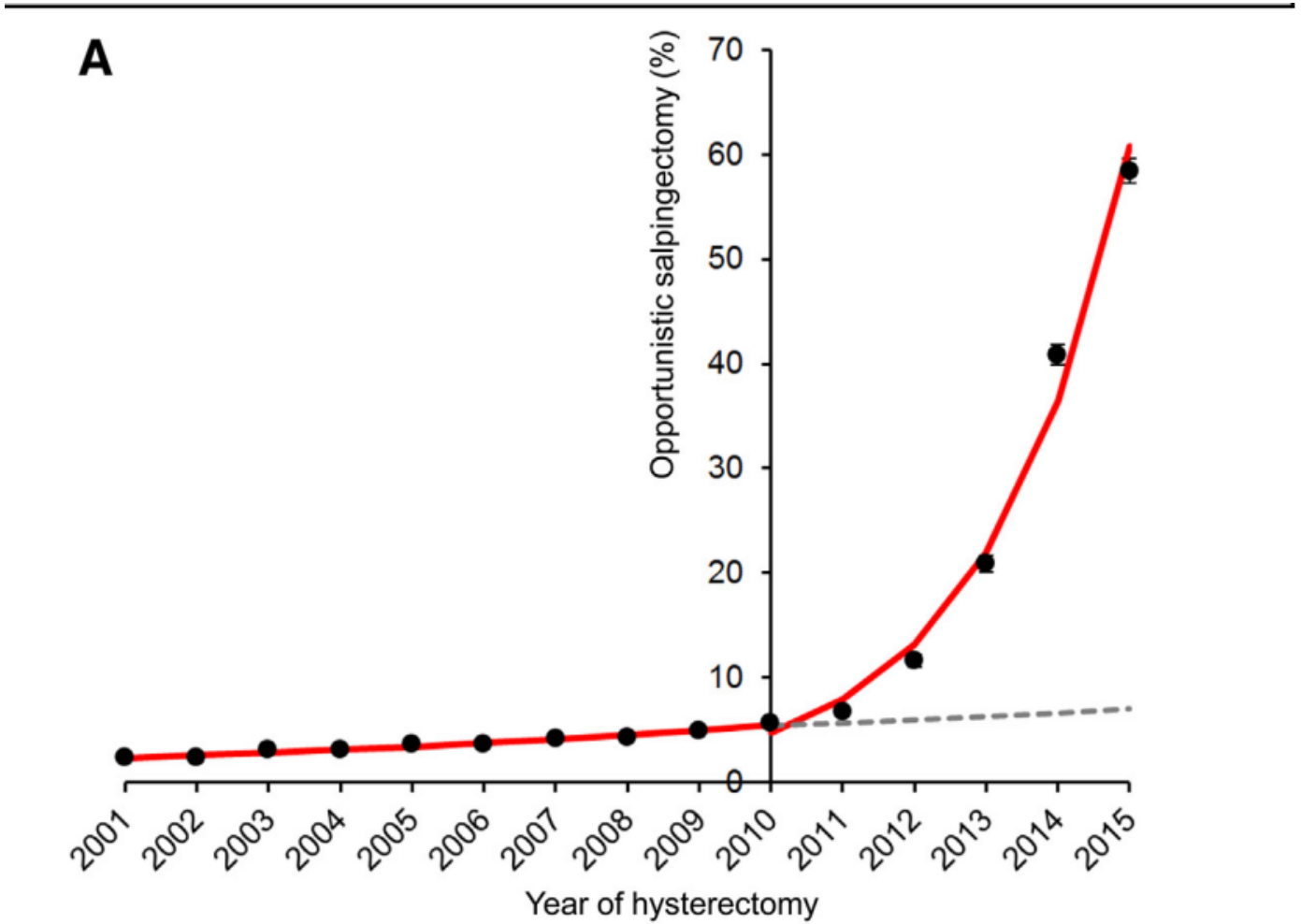
Committee on Gynecologic Practice

This Committee Opinion was developed by the American College of Obstetricians and Gynecologists' Committee on Gynecologic Practice in collaboration with committee member Lubna Chohan, MD and committee liaison Debra L. Richardson, MD.

Opportunistic Salpingectomy as a Strategy for Epithelial Ovarian Cancer Prevention

ABSTRACT: Opportunistic salpingectomy may offer obstetrician–gynecologists and other health care providers the opportunity to decrease the risk of ovarian cancer in their patients who are already undergoing pelvic surgery for benign disease. By performing salpingectomy when patients undergo an operation during which the fallopian tubes could be removed in addition to the primary surgical procedure (eg, hysterectomy), the risk of ovarian cancer is reduced. Although opportunistic salpingectomy offers the opportunity to significantly decrease the risk of ovarian cancer, it does not eliminate the risk of ovarian cancer entirely. Counseling women who are undergoing routine pelvic surgery about the risks and benefits of salpingectomy should include an informed consent discussion about the role of oophorectomy and bilateral salpingo-oophorectomy. Bilateral salpingo-oophorectomy that causes surgical menopause reduces the risk of ovarian cancer but may increase the risk of cardiovascular disease, cancer other than ovarian cancer, osteoporosis, cognitive impairment, and all-cause mor-

Rate of opportunistic salpingectomy in the USA



Nov 2020 AJOG

GYNECOLOGY

Paradigm shift from tubal ligation to opportunistic salpingectomy at cesarean delivery in the United States

Rachel S. Mandelbaum, MD; Shinya Matsuzaki, MD, PhD; Rauvynne N. Sangara, MD; Maximilian Klar, MD, MPH; Kazuhide Matsushima, MD; Lynda D. Roman, MD; Richard J. Paulson, MD; Jason D. Wright, MD; Koji Matsuo, MD, PhD

BACKGROUND: Opportunistic salpingectomy is now recommended at the time of routine gynecologic surgery to reduce the risk of future ovarian cancer, and performance of opportunistic salpingectomy has increased markedly at the time of benign hysterectomy. Salpingectomy has also been suggested to be feasible at the time of cesarean delivery in women desiring sterilization; however, uptake has not been previously studied on a national level.

OBJECTIVE: This study aimed to examine recent population trends in the utilization and characteristics of salpingectomy at the time of cesarean delivery in the United States.

STUDY DESIGN: This is a population-based retrospective observational study querying the National Inpatient Sample between October 2015 and December 2018. The primary outcome measure was the temporal trend of bilateral salpingectomy at cesarean delivery, assessed with linear segmented regression with log transformation utilizing 3-month time increments. The secondary outcome measures included patient characteristics associated with bilateral salpingectomy, assessed with a multinomial regression model, and surgical outcome (hemorrhage, blood transfusion, hysterectomy, and oophorectomy) at the time of bilateral salpingectomy vs bilateral tubal ligation, assessed with generalized estimating equation in a propensity score-matched model.

RESULTS: There were 3,813,823 women at the age of 15 to 49 years who had cesarean deliveries included, of whom 397,260 (10.4%) had

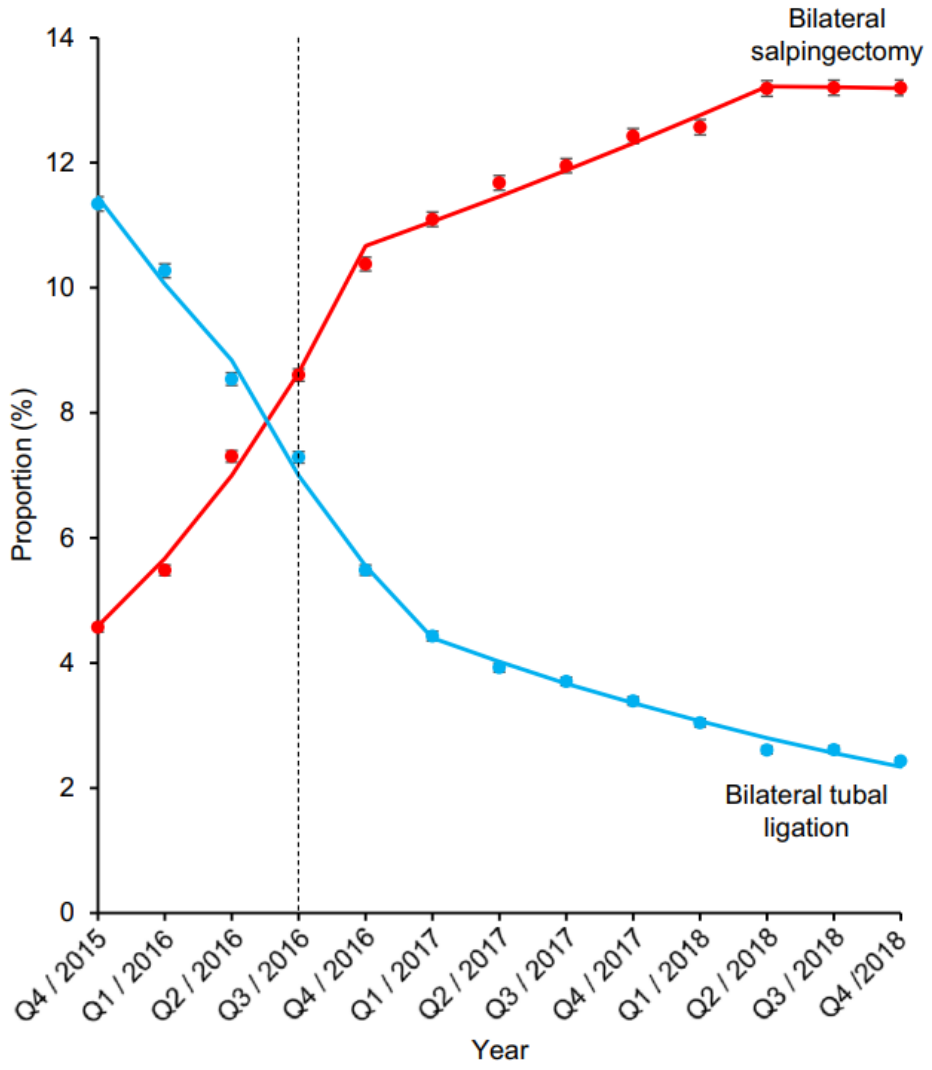
women undergoing cesarean delivery significantly decreased from 11.3% to 2.4% (odds ratio, 0.20; 95% confidence interval, 0.19–0.21). By the third quarter of 2016, the number of women who had bilateral salpingectomy exceeded those who had bilateral tubal ligation at cesarean delivery (8.6% vs 7.3%). Increasing the utilization of bilateral salpingectomy did not vary across age groups; the salpingectomy rate increased from 7.5% to 21.1% among women at the age of ≥35 years and from 3.8% to 10.7% among women at the age of <35 years (both, $P<.001$). In a propensity score matched model, women in the bilateral salpingectomy group were more likely to have hemorrhage (3.8% vs 3.1%; odds ratio, 1.24; 95% confidence interval, 1.15–1.33), blood product transfusion (2.1% vs 1.8%; odds ratio, 1.16; 95% confidence interval, 1.04–1.30), hysterectomy (0.8% vs 0.4%; odds ratio, 2.28; 95% confidence interval, 1.84–2.82), and oophorectomy (0.3% vs 0.2%; odds ratio, 2.02; 95% confidence interval, 1.47–2.79) than those in the bilateral tubal ligation group. When restricted to the nonhysterectomy cases, the bilateral salpingectomy group had a higher rate of hemorrhage (3.4% vs 3.0%; odds ratio, 1.16; 95% confidence interval, 1.06–1.26) and oophorectomy (0.3% vs 0.1%; odds ratio, 1.75; 95% confidence interval, 1.22–2.50) than the bilateral tubal ligation group.

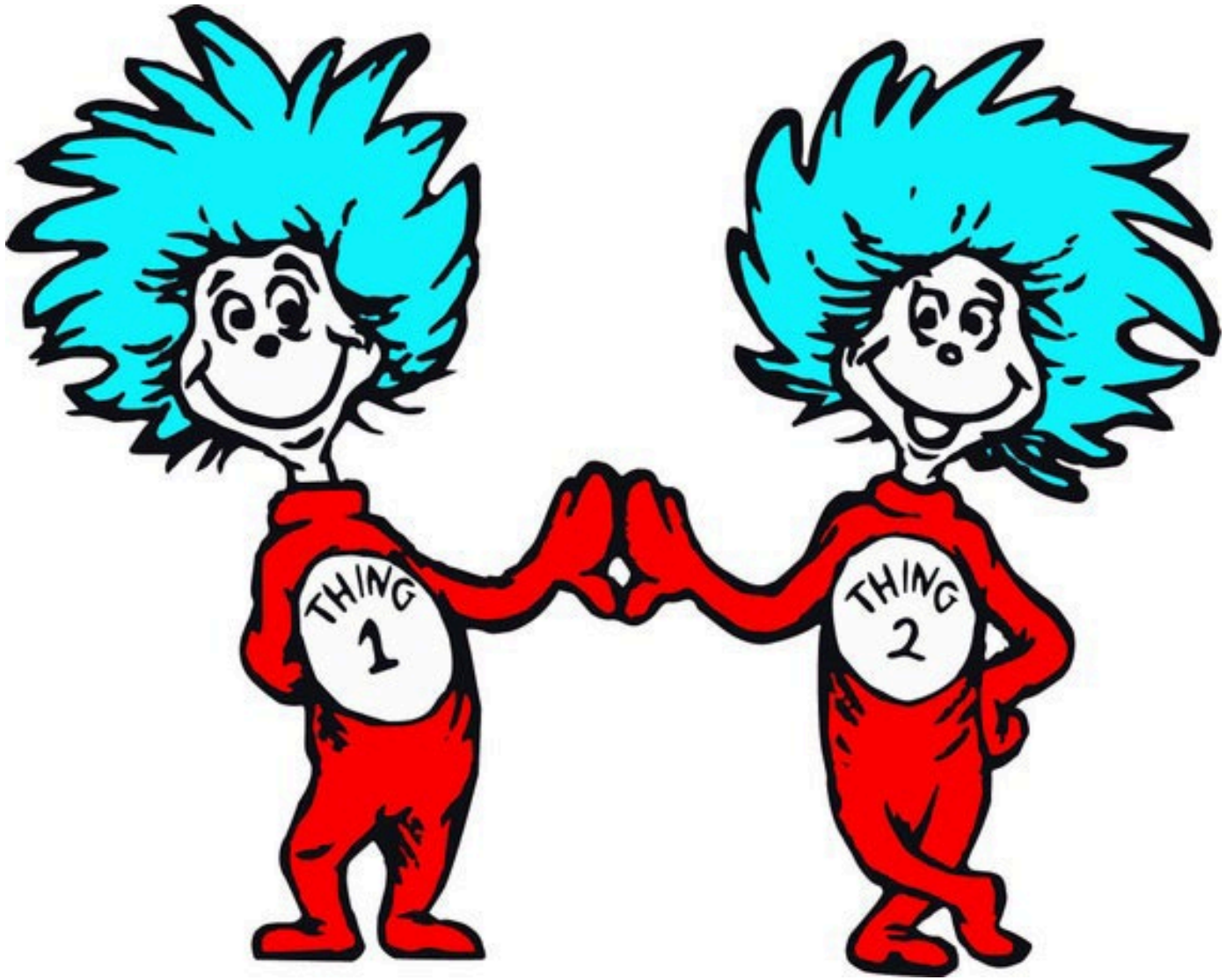
CONCLUSION: In the United States, the utilization of bilateral salpingectomy at the time of cesarean delivery increased rapidly between 2015 and 2018, replacing tubal ligation as the most common type of

AJOG Oct 2021

FIGURE 2

Trends of opportunistic salpingectomy and bilateral tubal ligation at cesarean delivery




THING
1
THING
2

Clinical trial

OPEN ACCESS

TUBectomy with delayed oophorectomy as an alternative to risk-reducing salpingo-oophorectomy in high-risk women to assess the safety of prevention: the TUBA-WISP II study protocol

Miranda P Steenbeek ,[1] Majke H D van Bommel ,[1] Joanna intHout,[2] Christine B Peterson,[3] Michiel Simons,[4] Kit C B Roes,[2] Marleen Kets,[5] Barbara M Norquist,[6] Elizabeth M Swisher,[6] Rosella P M G Hermens,[7] the TUBA-WISP II consortium,[8] Karen H Lu,[9] Joanne A de Hullu[1]

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ijgc-2023-004377).

For numbered affiliations see end of article.

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ABSTRACT

Background Risk-reducing salpingectomy with delayed oophorectomy has gained interest for individuals at high risk for tubo-ovarian cancer as there is compelling evidence that especially high-grade serous carcinoma originates in the fallopian tubes. Two studies have demonstrated a positive effect of salpingectomy on menopause-related quality of life and sexual health compared with standard risk-reducing salpingo-oophorectomy.

Primary Objective To investigate whether salpingectomy with delayed oophorectomy is non-inferior to the current standard salpingo-oophorectomy for the prevention of tubo-ovarian cancer among individuals at high inherited risk.

Primary Endpoint The primary outcome is the cumulative tubo-ovarian cancer incidence at the target age: 46 years for *BRCA1* and 51 years for *BRCA2* pathogenic variant carriers.

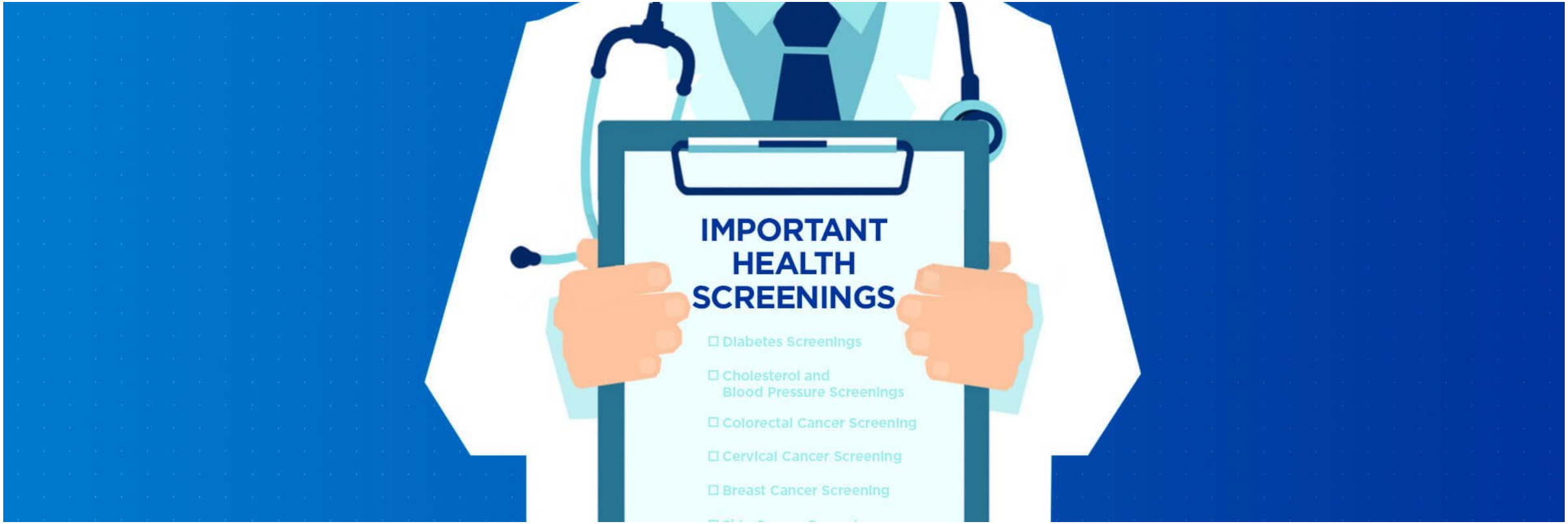
Sample size The sample size to ensure sufficient power to test non-inferiority of salpingectomy with delayed oophorectomy compared with salpingo-oophorectomy requires 1500 *BRCA1* and 1500 *BRCA2* pathogenic variant carriers.

Estimated Dates for Completing Accrual and Presenting Results Participant recruitment is expected to be completed at the end of 2026 (total recruitment period of 5 years). The primary outcome is expected to be available in 2036 (minimal follow-up period of 10 years).

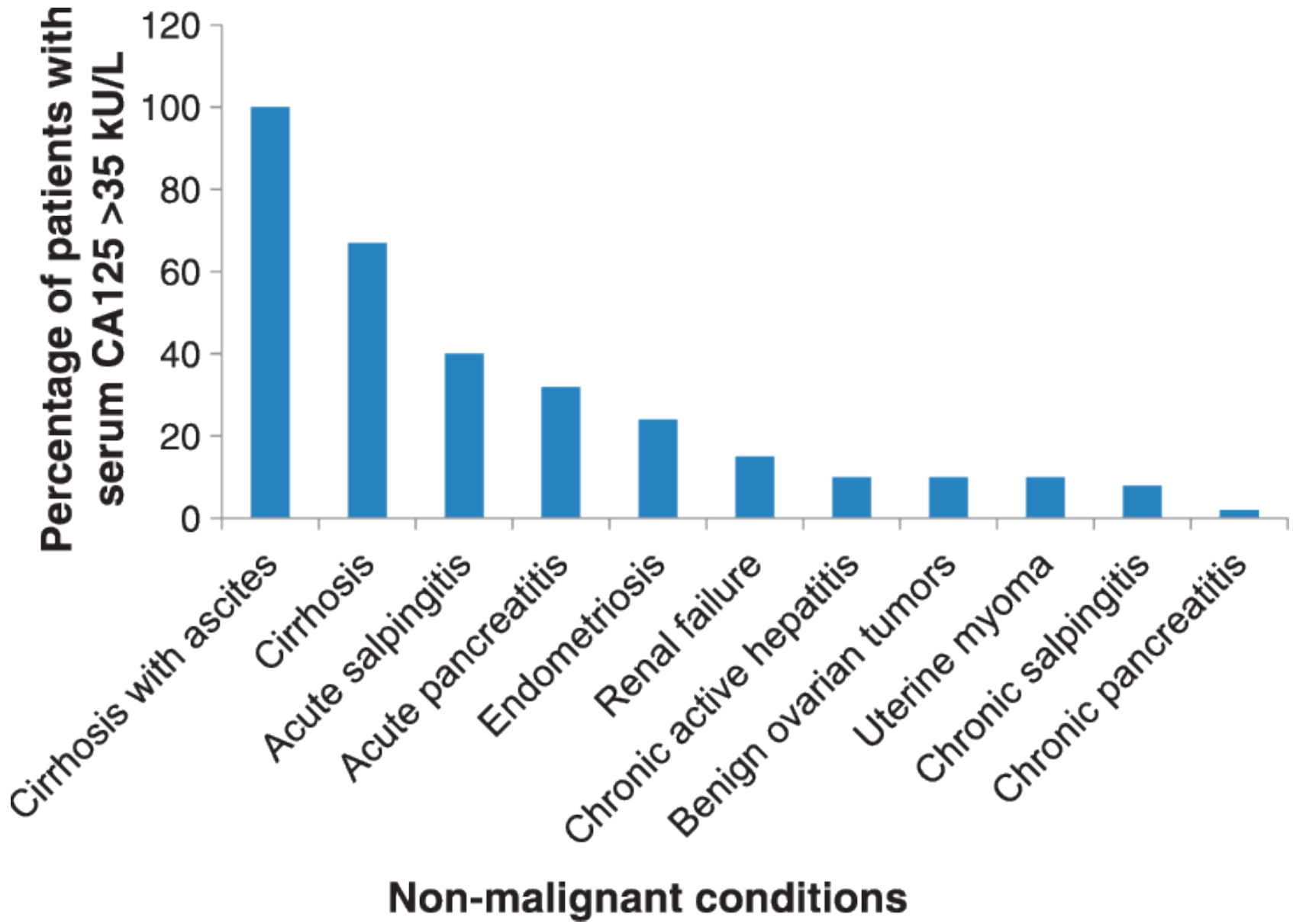
Trial Registration Number NCT04294927.

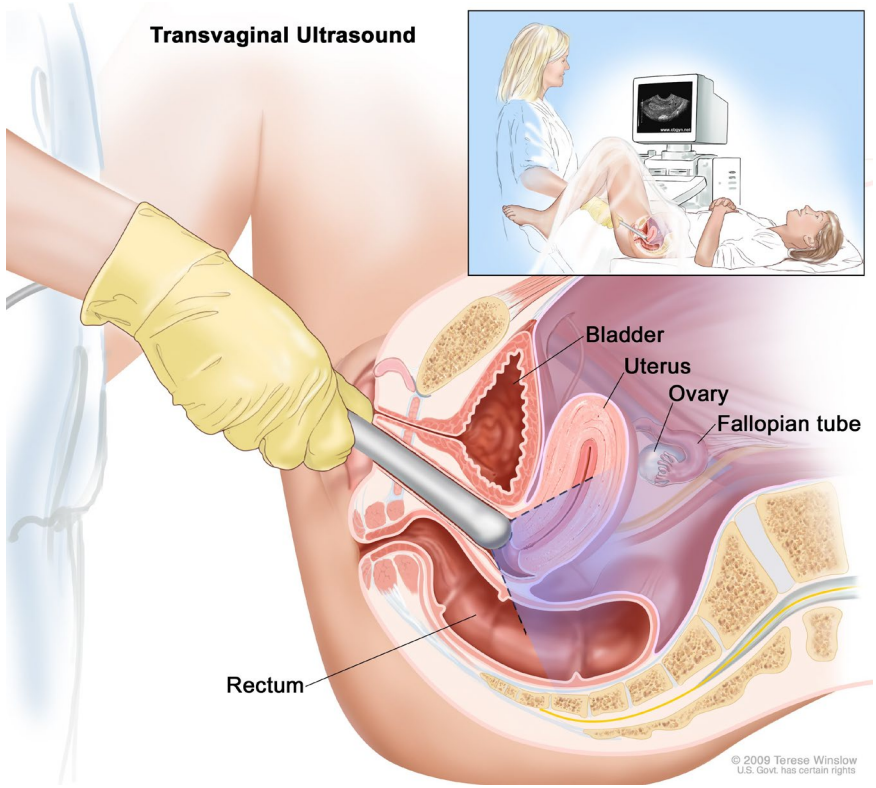
Educational objectives

1. An expanded knowledge base of why ovarian cancer is gradually decreasing year after year.
2. Appreciate the inability to effectively screen while being aware of early detection strategies.
3. Describe innovations in treatment that have led to dramatic improvements and unheard of cures.
4. Explore future paradigms of care and cutting-edge research to further improve outcomes.


IMPORTANT
HEALTH
SCREENINGS
Diabetes Screenings
Cholesterol and
Blood Pressure Screenings
Colorectal Cancer Screening
Cervical Cancer Screening
Breast Cancer Screening


CA 125
TUMOR MARKER
CA 125 - Test


Percentage of patients with serum CA125 >35 kU/L
120
100
80
60
40
20
0
Cirrhosis with ascites
Cirrhosis
Acute salpingitis
Acute pancreatitis
Endometriosis
Renal failure
Chronic active hepatitis
Benign ovarian tumors
Uterine myoma
Chronic salpingitis
Chronic pancreatitis
Non-malignant conditions


Transvaginal Ultrasound
Bladder
Uterus
Ovary
Fallopian tube
Rectum
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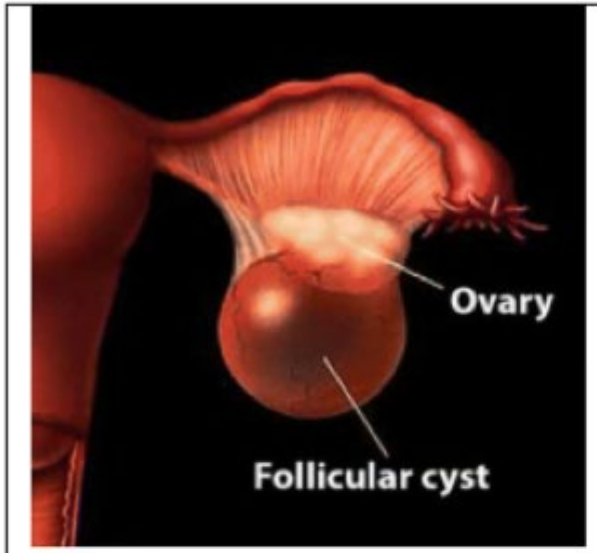
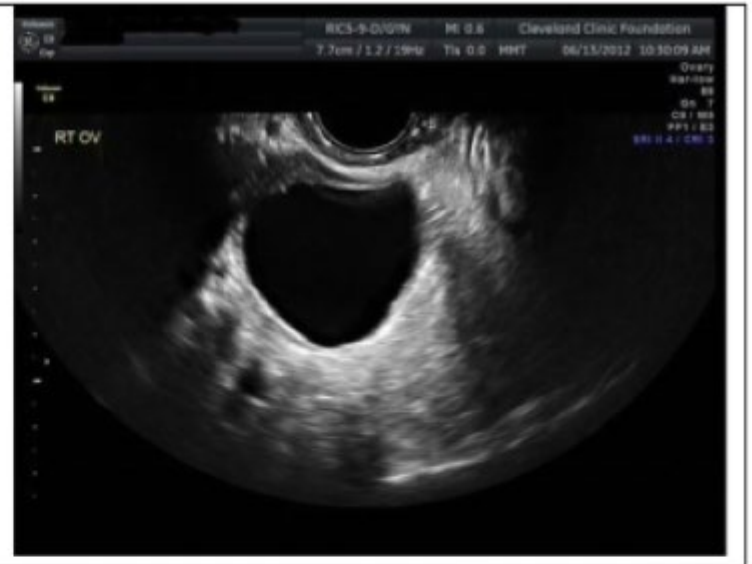
CA 125 - Test
CA 125
TUMOR MARKER

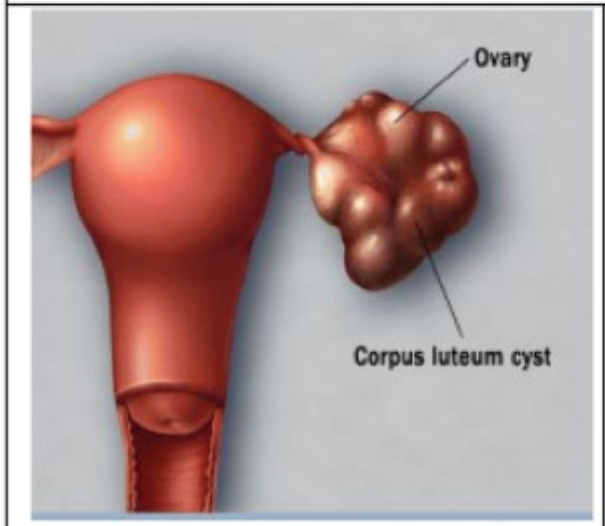
COMPLEX

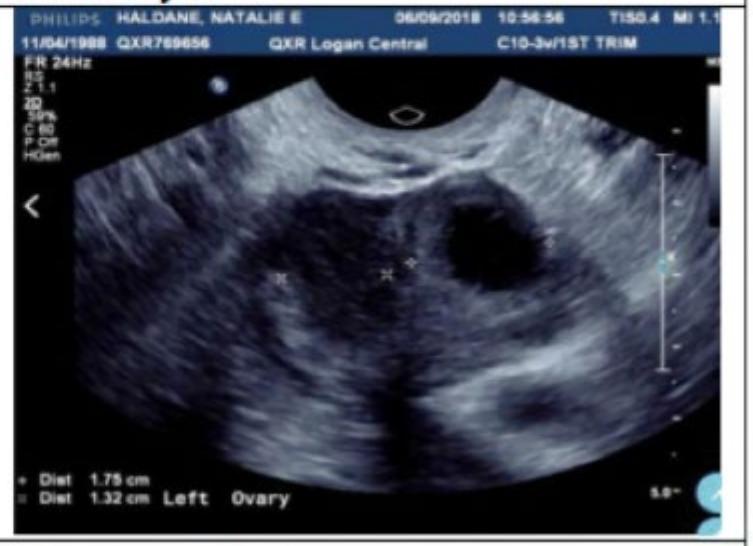
Normally 2-5 cm





Follicle Cyst





Corpus Luteum Cyst

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

IMPORTANCE Ovarian cancer is relatively rare but the fifth-leading cause of cancer mortality among United States women.

OBJECTIVE To systematically review evidence on benefits and harms of ovarian cancer screening among average-risk women to inform the United States Preventive Services Task Force.

DATA SOURCES MEDLINE, PubMed, Cochrane Collaboration Registry of Controlled Trials; studies published in English from January 1, 2003, through January 31, 2017; ongoing surveillance in targeted publications through November 22, 2017.

STUDY SELECTION Randomized clinical trials of ovarian cancer screening in average-risk women that reported mortality or quality-of-life outcomes. Interventions included transvaginal ultrasound, cancer antigen 125 (CA-125) testing, or their combination. Comparators were usual care or no screening.

DATA EXTRACTION AND SYNTHESIS Independent critical appraisal and data abstraction by 2 reviewers. Meta-analytic pooling of results was not conducted because of the small number of studies and heterogeneity of interventions.

MAIN OUTCOMES AND MEASURES Ovarian cancer mortality, false-positive screening results and surgery, surgical complications, and psychological effects of screening.

Editorial page 557

Related article page 588 and JAMA Patient Page page 624

Supplemental content

Related articles at jamaoncology.com, jamainternalmedicine.com

JAMA. 2018;319(6):595-606.

CONCLUSIONS AND RELEVANCE

In randomized trials conducted among average-risk, asymptomatic women, ovarian cancer mortality did ***not*** significantly differ between screened women and those with no screening or in usual care. Screening harms included surgery (with major surgical complications) in women found to not have cancer. Further research is needed to identify effective approaches for reducing ovarian cancer incidence and mortality

Published in final edited form as:
Gynecol Oncol. 2012 February ; 124(2): 230–235. doi:10.1016/j.ygyno.2011.10.032.

Symptom Triggered Screening for Ovarian Cancer: A Pilot Study of Feasibility and Acceptability

Barbara A. Goff, MD[1], **Kimberly A. Lowe, PhD**[3,4], **Jeannette C. Kane, RN2, BSN**[1], **Marissa D. Robertson**[1], **Marcia A. Gaul**[2], and **M. Robyn Andersen, PhD**[2,3]

[1]University of Washington, Department of Obstetrics and Gynecology, Seattle WA

[2]Fred Hutchinson Cancer Research Center, Molecular Diagnostics Program, Seattle WA

[3]University of Washington, School of Public Health, Seattle WA

[4]Exponent Health Sciences, Seattle WA

Abstract

Purpose—Our goal was to determine if symptom-based ovarian cancer screening was feasible in a primary care clinic and acceptable to women and practitioners. In addition, we wanted to describe the outcomes for a pilot group of screened women.

Methods—A prospective study of 2262 women over age 40 with at least one ovary participated in symptom-based screening using a symptom index (SI). The first 1001 were in a non-

BEST PRACTICES IN ONCOLOGY: RECOMMENDATIONS FROM THE CHOOSING WISELY CAMPAIGN

Recommendation	*Sponsoring organization*
Do not screen for ovarian cancer in asymptomatic women at average risk.	American College of Obstetricians and Gynecologists
Do not screen low-risk women with cancer antigen (CA) 125 or ultrasound for ovarian cancer.	Society of Gynecologic Oncology

Source: For more information on the Choosing Wisely Campaign, see http://www.choosingwisely.org. For supporting citations and to search Choosing Wisely recommendations relevant to primary care, see http://www.aafp.org/afp/recommendations/search.htm.

Screening

Educational objectives

1. An expanded knowledge base of why ovarian cancer is gradually decreasing year after year.
2. Appreciate the inability to effectively screen while being aware of early detection strategies.
3. Describe innovations in treatment that have led to dramatic improvements and unheard of cures.
4. Explore future paradigms of care and cutting-edge research to further improve outcomes.

VOLUME 27 · NUMBER 9 · MARCH 20 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Evaluation of New Platinum-Based Treatment Regimens in Advanced-Stage Ovarian Cancer: A Phase III Trial of the Gynecologic Cancer InterGroup

Michael A. Bookman, Mark F. Brady, William P. McGuire, Peter G. Harper, David S. Alberts, Michael Friedlander, Nicoletta Colombo, Jeffrey M. Fowler, Peter A. Argenta, Koen De Geest, David G. Mutch, Robert A. Burger, Ann Marie Swart, Edward L. Trimble, Chrisann Accario-Winslow, and Lawrence M. Roth

From the Fox Chase Cancer Center, Philadelphia, PA; Gynecologic Oncology Group Statistical and Data Center, Buffalo, NY; Franklin Square Hospital; Baltimore, MD; Guy's Hospital, London, United Kingdom; Arizona Cancer Center, Tucson, AZ; Australia New Zealand Gynaecological Oncology Group, Camperdown, Australia; European Institute of Cancer Research, Milano, Italy; Ohio State University, Columbus, OH; University of Minnesota School of Medicine, Minneapolis, MN; University of Iowa Hospitals and Clinics, Iowa City, IA; Washington University School of Medicine, St. Louis, MO; University of California, Irvine Medical Center, Orange, CA; University College London and Medical Research Council Clinical Trials Unit, London, United Kingdom; National Cancer Institute, Bethesda, MD; and Indiana University School of Medicine, Indianapolis, IN.

Submitted July 16, 2008; accepted November 11, 2008; published online ahead of print at www.jco.org on February 17, 2009.

Supported by National Cancer Institute Grants No. CA 27469 to the Gyneco-

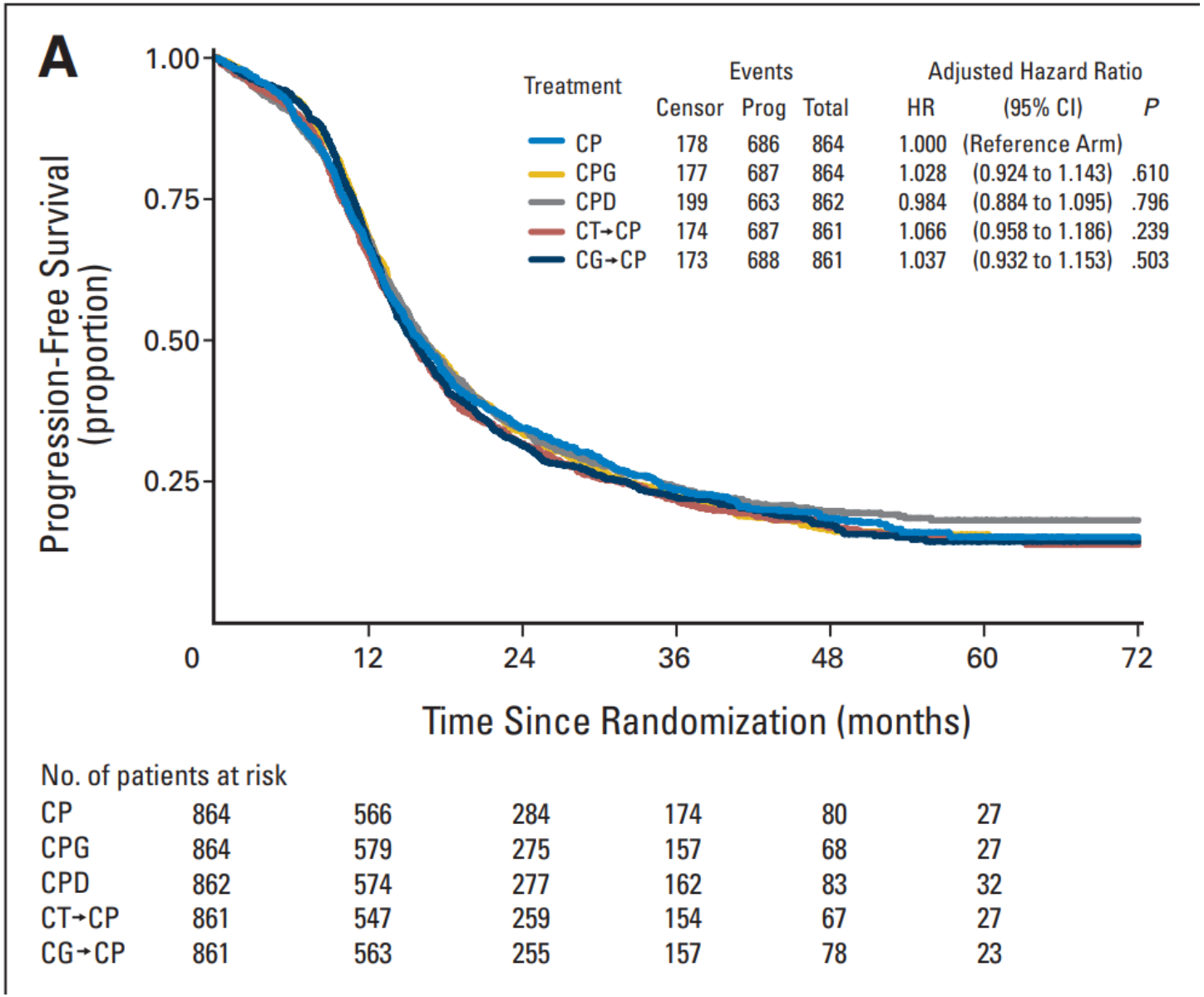
ABSTRACT

Purpose
To determine if incorporation of an additional cytotoxic agent improves overall survival (OS) and progression-free survival (PFS) for women with advanced-stage epithelial ovarian carcinoma (EOC) and primary peritoneal carcinoma who receive carboplatin and paclitaxel.

Patients and Methods
Women with stages III to IV disease were stratified by coordinating center, maximal diameter of residual tumor, and intent for interval cytoreduction and were then randomly assigned among five arms that incorporated gemcitabine, methoxypolyethylene glycosylated liposomal doxorubicin, or topotecan compared with carboplatin and paclitaxel. The primary end point was OS and was determined by pairwise comparison to the reference arm, with a 90% chance of detecting a true hazard ratio of 1.33 that limited type I error to 5% (two-tail) for the four comparisons.

Results
Accrual exceeded 1,200 patients per year. An event-triggered interim analysis occurred after 272 events on the reference arm, and the study closed with 4,312 women enrolled. Arms were well balanced for demographic and prognostic factors, and 79% of patients completed eight cycles of therapy. There were no improvements in either PFS or OS associated with any experimental regimen. Survival analyses of groups defined by size of residual disease also failed to show experimental benefit in any subgroup

- 4312 pts enrolled
- 5 arm trial
- Lack of novelty
- Jan 2001 start


A
1.00
0.75
0.50
0.25
0
12
24
36
48
60
72
Progression-Free Survival (proportion)
Time Since Randomization (months)
Treatment
Events
Censor Prog Total
Adjusted Hazard Ratio
HR (95% CI) P
CP 178 686 864 1.000 (Reference Arm)
CPG 177 687 864 1.028 (0.924 to 1.143) .610
CPD 199 663 862 0.984 (0.884 to 1.095) .796
CT→CP 174 687 861 1.066 (0.958 to 1.186) .239
CG→CP 173 688 861 1.037 (0.932 to 1.153) .503
No. of patients at risk
CP 864 566 284 174 80 27
CPG 864 579 275 157 68 27
CPD 862 574 277 162 83 32
CT→CP 861 547 259 154 67 27
CG→CP 861 563 255 157 78 23

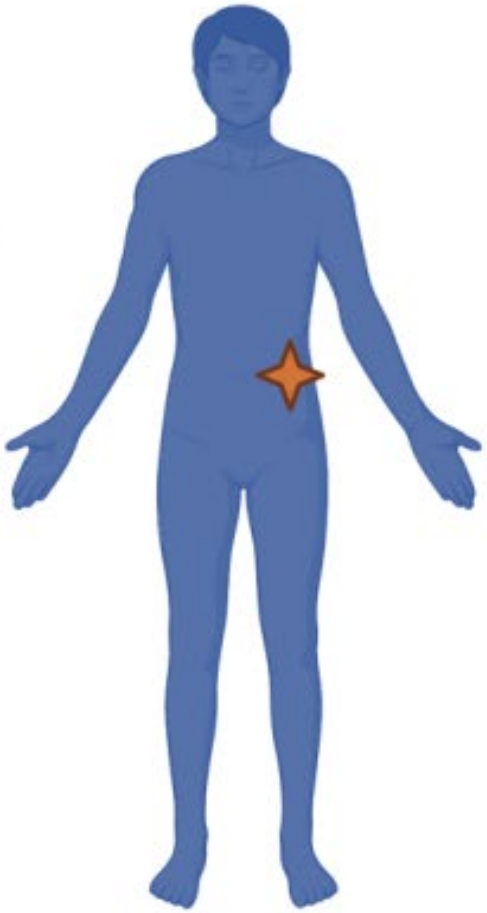

The Dark Ages

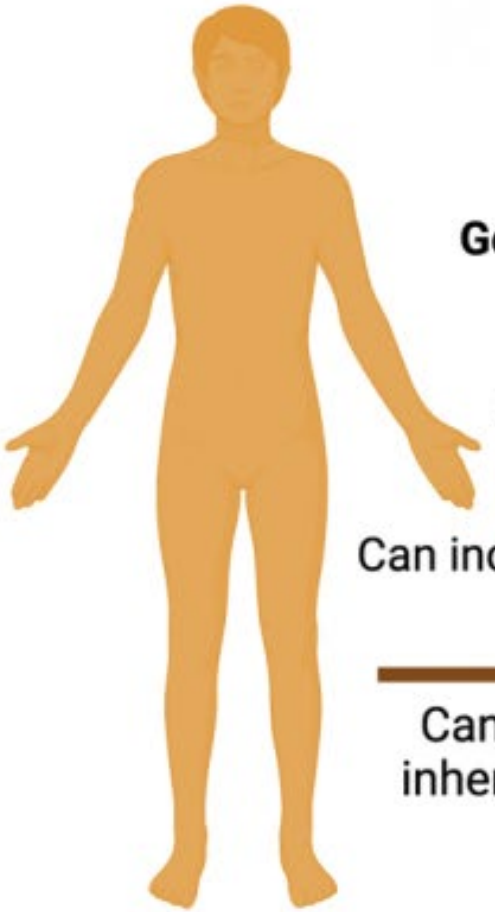
Somatic DNA changes

Acquired over a persons lifetime in single cells

Can lead to cancer

Can NOT be inherited



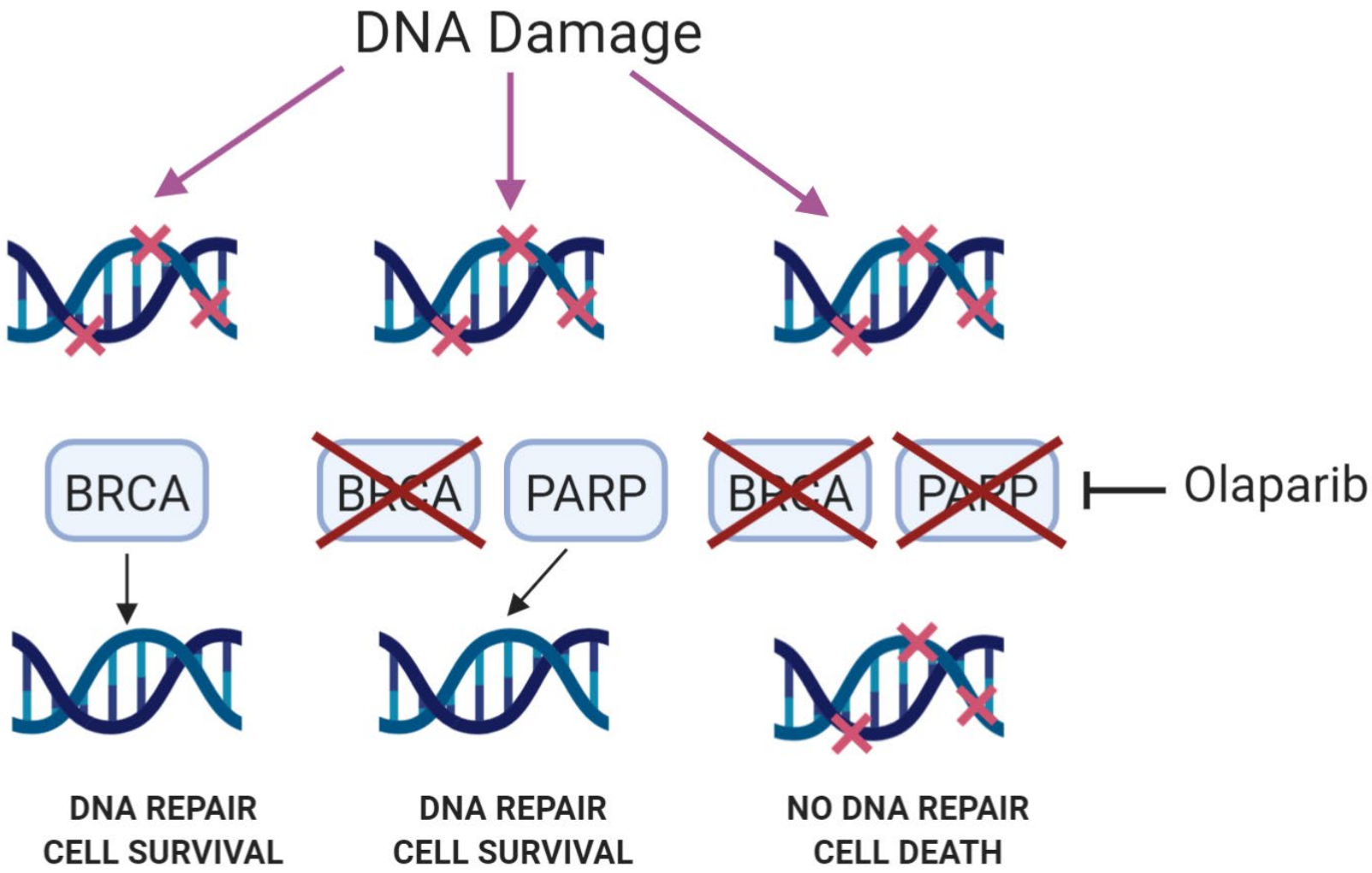


Germline DNA changes

Present in every cell of the body including egg and sperm

Can increase cancer susceptibility

Can be inherited


DNA Damage
BRCA
BRCA
PARP
BRCA
PARP
Olaparib
DNA REPAIR
CELL SURVIVAL
DNA REPAIR
CELL SURVIVAL
NO DNA REPAIR
CELL DEATH

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 27, 2018 VOL. 379 NO. 26

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

K. Moore, N. Colombo, G. Scambia, B.-G. Kim, A. Oaknin, M. Friedlander, A. Lisyanskaya, A. Floquet, A. Leary, G.S. Sonke, C. Gourley, S. Banerjee, A. Oza, A. González-Martín, C. Aghajanian, W. Bradley, C. Mathews, J. Liu, E.S. Lowe, R. Bloomfield, and P. DiSilvestro

ABSTRACT

BACKGROUND

Most women with newly diagnosed advanced ovarian cancer have a relapse within 3 years after standard treatment with surgery and platinum-based chemotherapy. The benefit of the oral poly(adenosine diphosphate–ribose) polymerase inhibitor olaparib in relapsed disease has been well established, but the benefit of olaparib as maintenance therapy in newly diagnosed disease is uncertain.

METHODS

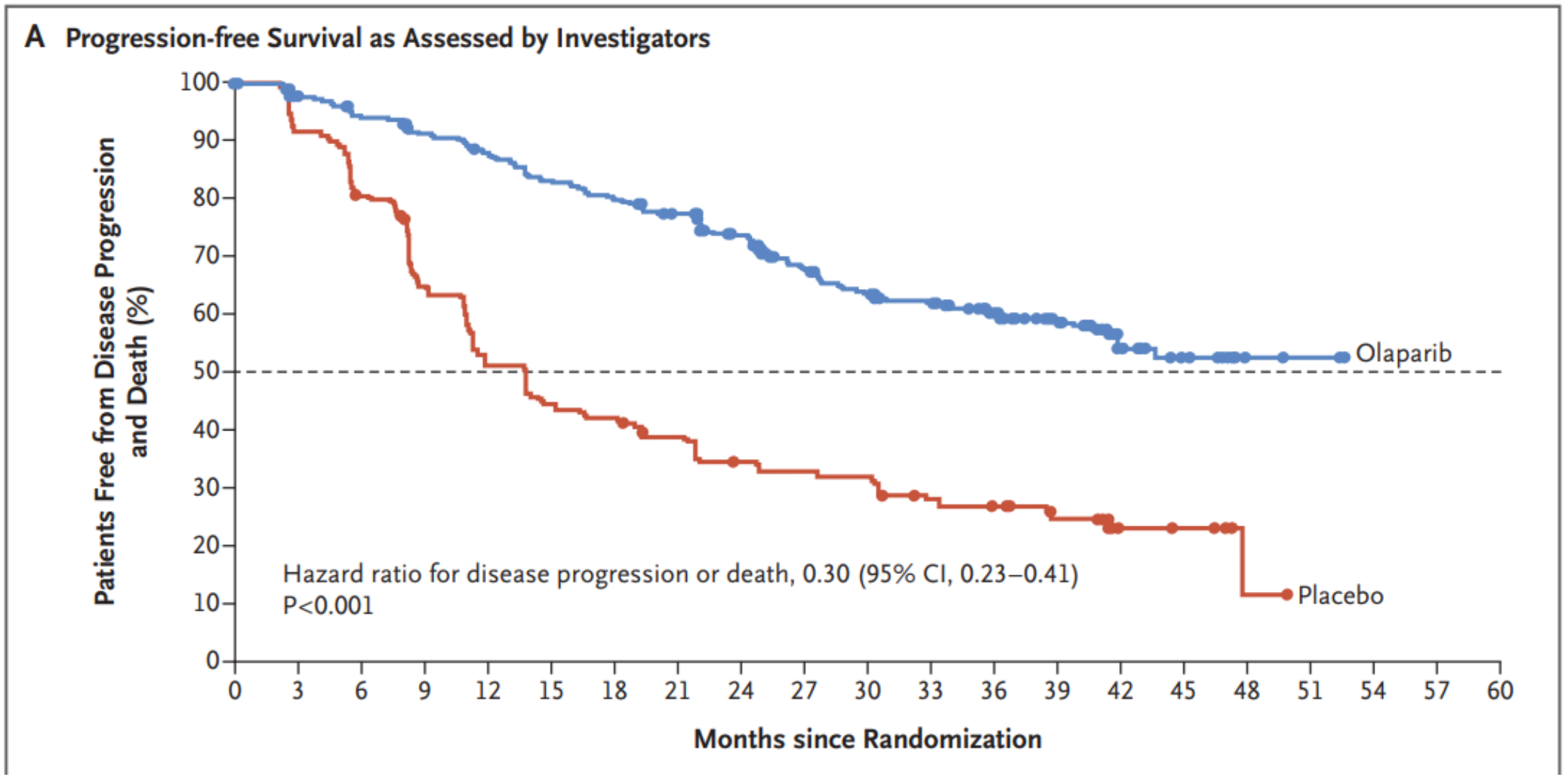
We conducted an international, randomized, double-blind, phase 3 trial to evaluate the efficacy of olaparib as maintenance therapy in patients with newly diagnosed advanced (International Federation of Gynecology and Obstetrics stage III or IV) high-grade serous or endometrioid ovarian cancer, primary peritoneal cancer, or fallopian-tube cancer (or a combination thereof) with a mutation in *BRCA1*, *BRCA2*,

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Moore at the Stephenson Cancer Center at the University of Oklahoma, 800 NE 10th St., Oklahoma City, OK 73104, or at kathleen-moore@ouhsc.edu.

This article was published on October 21, 2018, at NEJM.org.

N Engl J Med 2018;379:2495-505.
DOI: 10.1056/NEJMoa1810858

- 392 pts enrolled
- 2:1 randomization
- Somatic/germline
- Sept 2013 start


A Progression-free Survival as Assessed by Investigators
Patients Free from Disease Progression and Death (%)
100
90
80
70
60
50
40
30
20
10
0
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60
Months since Randomization
Olaparib
Placebo
Hazard ratio for disease progression or death, 0.30 (95% CI, 0.23–0.41)
P<0.001

Educational objectives

1. An expanded knowledge base of why ovarian cancer is gradually decreasing year after year.
2. Appreciate the inability to effectively screen while being aware of early detection strategies.
3. Describe innovations in treatment that have led to dramatic improvements and unheard of cures.
4. Explore future paradigms of care and cutting-edge research to further improve outcomes.

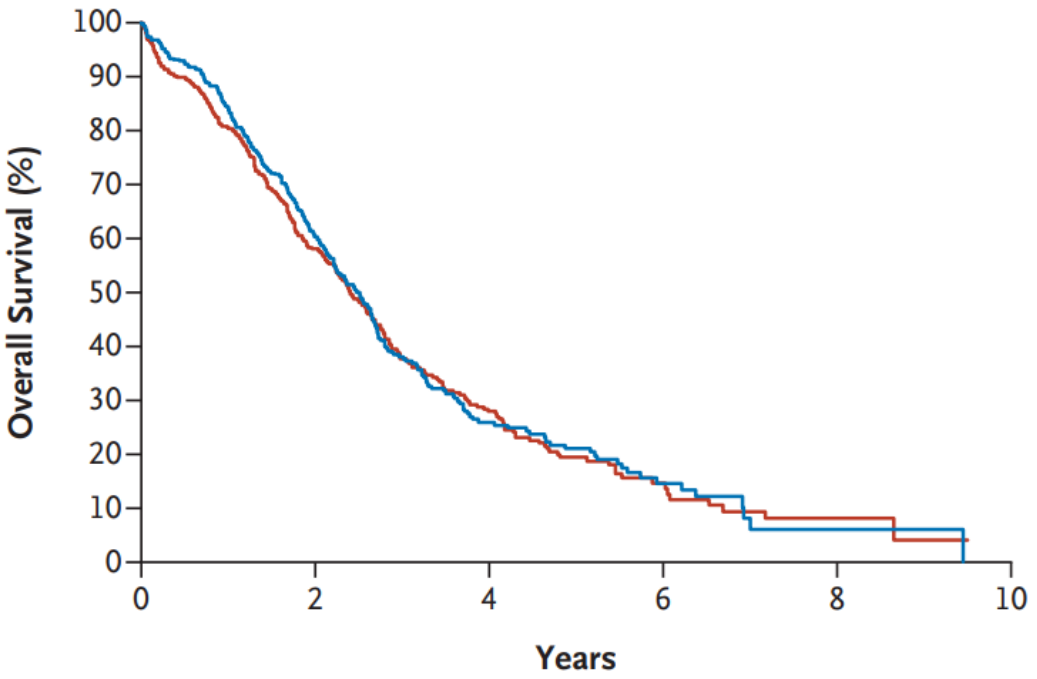
Neoadjuvant Chemotherapy or Primary Surgery in Stage IIIC or IV Ovarian Cancer

Ignace Vergote, M.D., Ph.D., Claes G. Tropé, M.D., Ph.D., Frédéric Amant, M.D., Ph.D., Gunnar B. Kristensen, M.D., Ph.D., Tom Ehlen, M.D., Nick Johnson, M.D., René H.M. Verheijen, M.D., Ph.D., Maria E.L. van der Burg, M.D., Ph.D., Angel J. Lacave, M.D., Pierluigi Benedetti Panici, M.D., Ph.D., Gemma G. Kenter, M.D., Ph.D., Antonio Casado, M.D., Cesar Mendiola, M.D., Ph.D., Corneel Coens, M.Sc., Leen Verleye, M.D., Gavin C.E. Stuart, M.D., Sergio Pecorelli, M.D., Ph.D., and Nick S. Reed, M.D., for the European Organization for Research and Treatment of Cancer–Gynaecological Cancer Group and the NCIC Clinical Trials Group* — a Gynecologic Cancer Intergroup Collaboration

- 718 pts with stage IIIC or IV EOC
- Postop death 2.5% v 0.7%
- R1 rate 40% v 80%

NEJM 2010;363:943-53.

A Intention-to-Treat Analysis



	No. of Events	No. of Patients at Risk				
Primary Debulking Surgery (PDS)	253	336	189	62	14	2
Neoadjuvant Chemo-therapy (NACT)	245	334	195	46	13	2

Primary chemotherapy versus primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial

Sean Kehoe, Jane Hook, Matthew Nankivell, Gordon C Jayson, Henry Kitchener, Tito Lopes, David Luesley, Timothy Perren, Selina Bannoo, Monica Mascarenhas, Stephen Dobbs, Sharadah Essapen, Jeremy Twigg, Jonathan Herod, Glenn McCluggage, Mahesh Parmar, Ann-Marie Swart

Summary

Background The international standard of care for women with suspected advanced ovarian cancer is surgical debulking followed by platinum-based chemotherapy. We aimed to establish whether use of platinum-based primary chemotherapy followed by delayed surgery was an effective and safe alternative treatment regimen.

Methods In this phase 3, non-inferiority, randomised, controlled trial (CHORUS) undertaken in 87 hospitals in the UK and New Zealand, we enrolled women with suspected stage III or IV ovarian cancer. We randomly assigned women (1:1) either to undergo primary surgery followed by six cycles of chemotherapy, or to three cycles of primary chemotherapy, then surgery, followed by three more cycles of completion chemotherapy. Each 3-week cycle consisted of carboplatin AUC5 or AUC6 plus paclitaxel 175 mg/m^2, or an alternative carboplatin combination regimen, or carboplatin monotherapy. We did the random assignment by use of a minimisation method with a random element, and stratified participants according to the randomising centre, largest radiological tumour size, clinical stage, and prespecified chemotherapy regimen. Patients and investigators were not masked to group assignment. The primary outcome measure was overall survival. Primary analyses were done in the intention-to-treat population. To establish non-inferiority, the upper bound of a one-sided 90% CI for the hazard ratio (HR) had to be less than 1·18. This trial is registered, number ISRCTN74802813, and is closed to new participants.

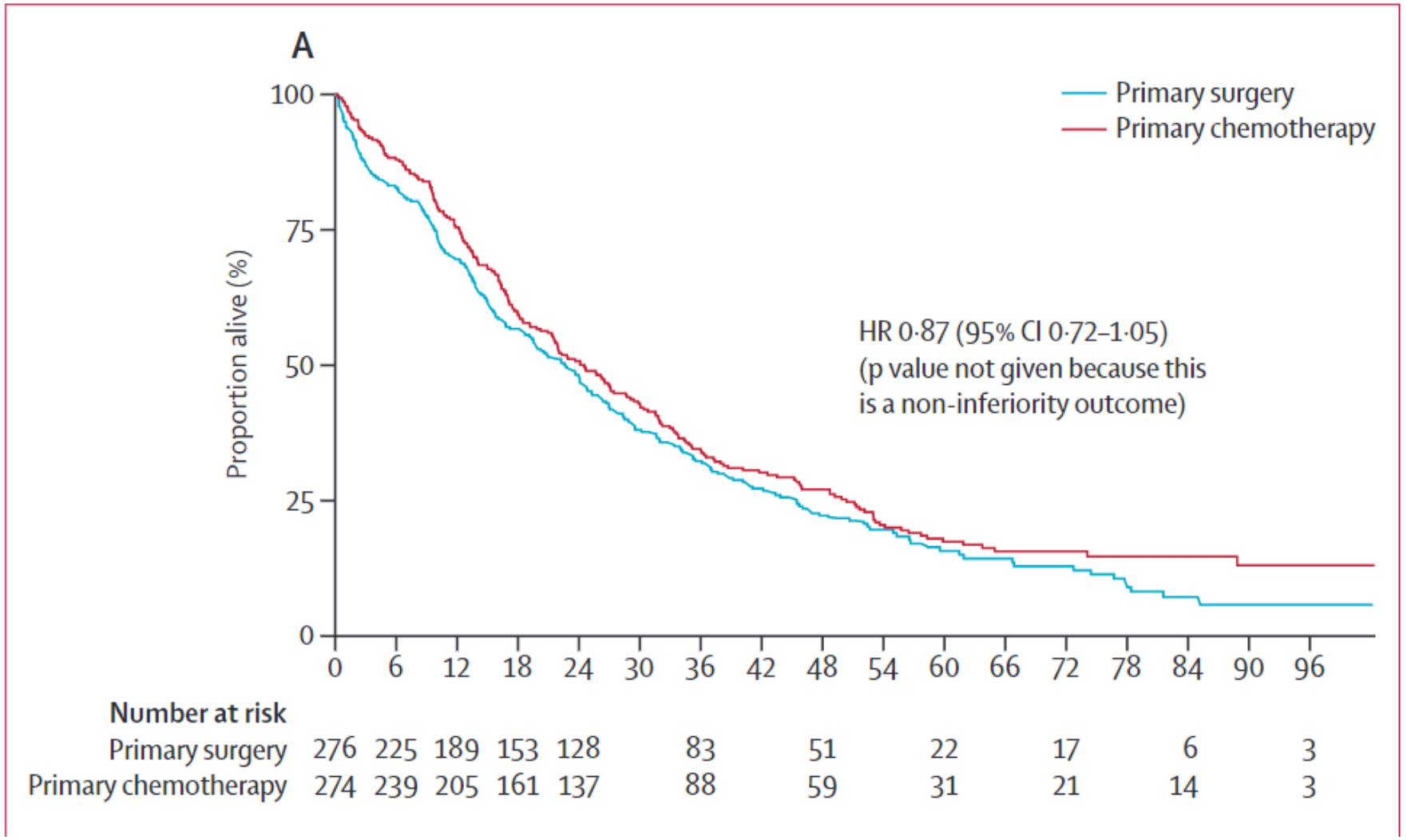
Findings Between March 1, 2004, and Aug 30, 2010, we randomly assigned 552 women to treatment. Of the 550 women who were eligible, 276 were assigned to primary surgery and 274 to primary chemotherapy. All were included in the intention-to-treat analysis; 251 assigned to primary surgery and 253 to primary chemotherapy were included in the per-protocol analysis. As of May 31, 2014, 451 deaths had occurred: 231 in the primary-surgery

Lancet 2015; 386: 249–57

Published Online
May 20, 2015
http://dx.doi.org/10.1016/S0140-6736(14)62223-6

See Comment page 223

School of Cancer Sciences, University of Birmingham, Birmingham, UK (Prof S Kehoe MD); **Medical Research Council Clinical Trials Unit, University College London, London, UK** (J Hook MRCP, M Nankivell MSc, S Bannoo MSc, M Mascarenhas PhD, Prof M Parmar DPhil, Prof A-M Swart MSc); **Department of Medical Oncology, Christie Hospital and University of Manchester, Manchester Academic Health Sciences Centre, Manchester, UK** (Prof G C Jayson FRCP); **Institute of Cancer Sciences, University of Manchester**


A
Primary surgery
Primary chemotherapy
Proportion alive (%)
100
75
50
25
0
HR 0·87 (95% CI 0·72–1·05)
(p value not given because this
is a non-inferiority outcome)
0 6 12 18 24 30 36 42 48 54 60 66 72 78 84 90 96
Number at risk
Primary surgery 276 225 189 153 128 83 51 22 17 6 3
Primary chemotherapy 274 239 205 161 137 88 59 31 21 14 3

Original Research

Laparoscopy Compared With Laparotomy for Debulking Ovarian Cancer After Neoadjuvant Chemotherapy

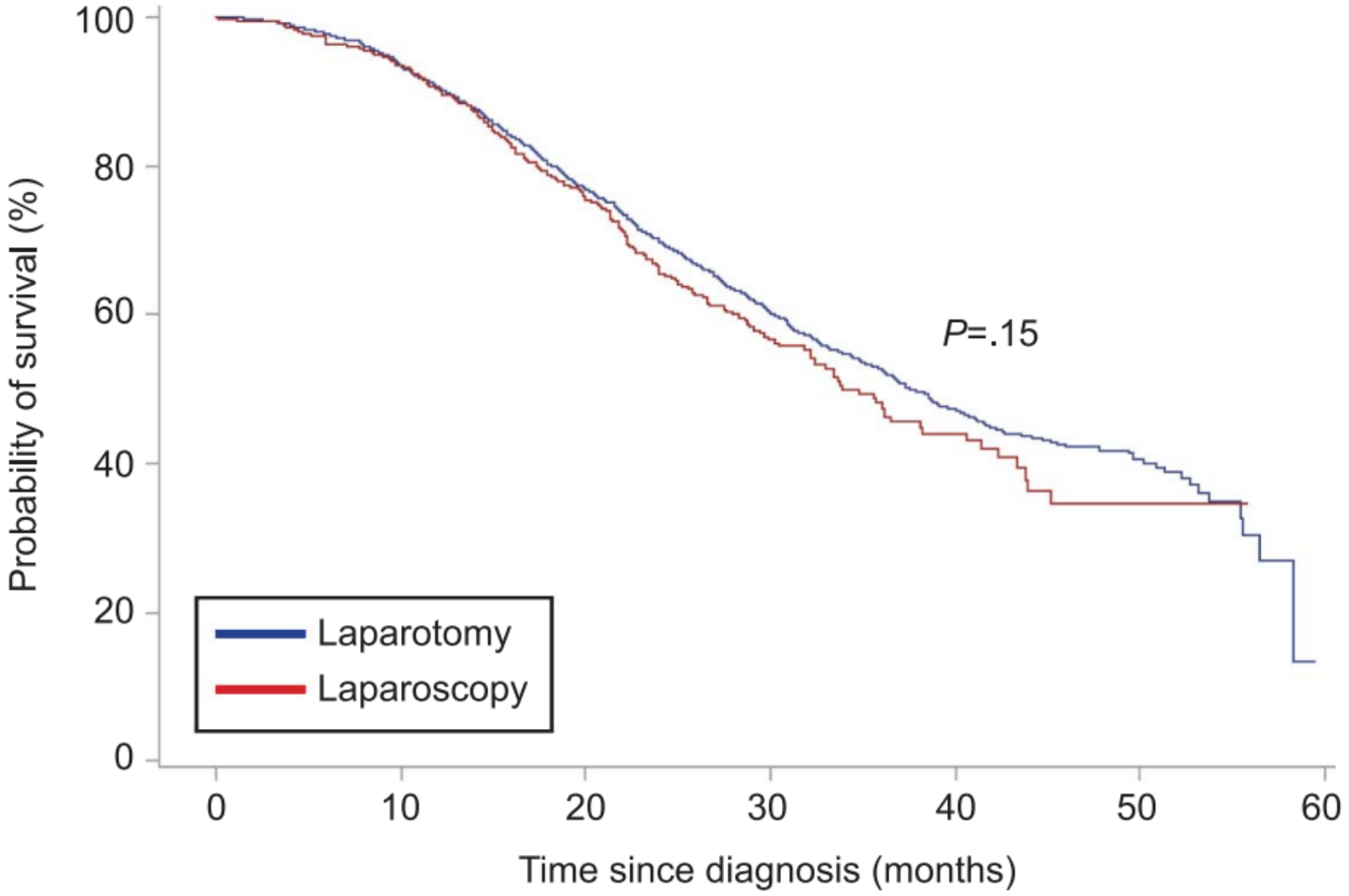
Alexander Melamed, MD, MPH, Roni Nitecki, MD, David M. Boruta II, MD, Marcela G. del Carmen, MD, MPH, Rachel M. Clark, MD, Whitfield B. Growdon, MD, Annekathryn Goodman, MD, John O. Schorge, MD, and J. Alejandro Rauh-Hain, MD

OBJECTIVE: To compare 3-year survival, length of hospitalization, perioperative mortality, risk of readmission, and residual disease associated with laparoscopic and laparotomic interval debulking surgery among women with epithelial ovarian cancer.

METHODS: We used the National Cancer Database to identify a cohort of patients diagnosed with stage IIIC and IV epithelial ovarian cancer between 2010 and 2012 who underwent neoadjuvant chemotherapy and interval debulking surgery. We compared 3-year overall survival, duration of postoperative hospitalization, 90-day post-

RESULTS: We identified 3,071 women meeting inclusion criteria, of whom 450 (15%) underwent surgery initiated laparoscopically. There was no difference in 3-year survival between patients undergoing laparoscopy [47.5%; 95% confidence interval (CI) 41.4–53.5] and laparotomy (52.6%; 95% CI 50.3–55.0; P=.12). Survival did not differ after adjustment for demographic characteristics, facility type, presence of comorbidities, and stage (adjusted hazard ratio, 1.09; 95% CI 0.93–1.28; P=.26). Postoperative hospitalization was slightly shorter in the laparoscopy group (median 4 compared with 5 days, P<.001). Fre-

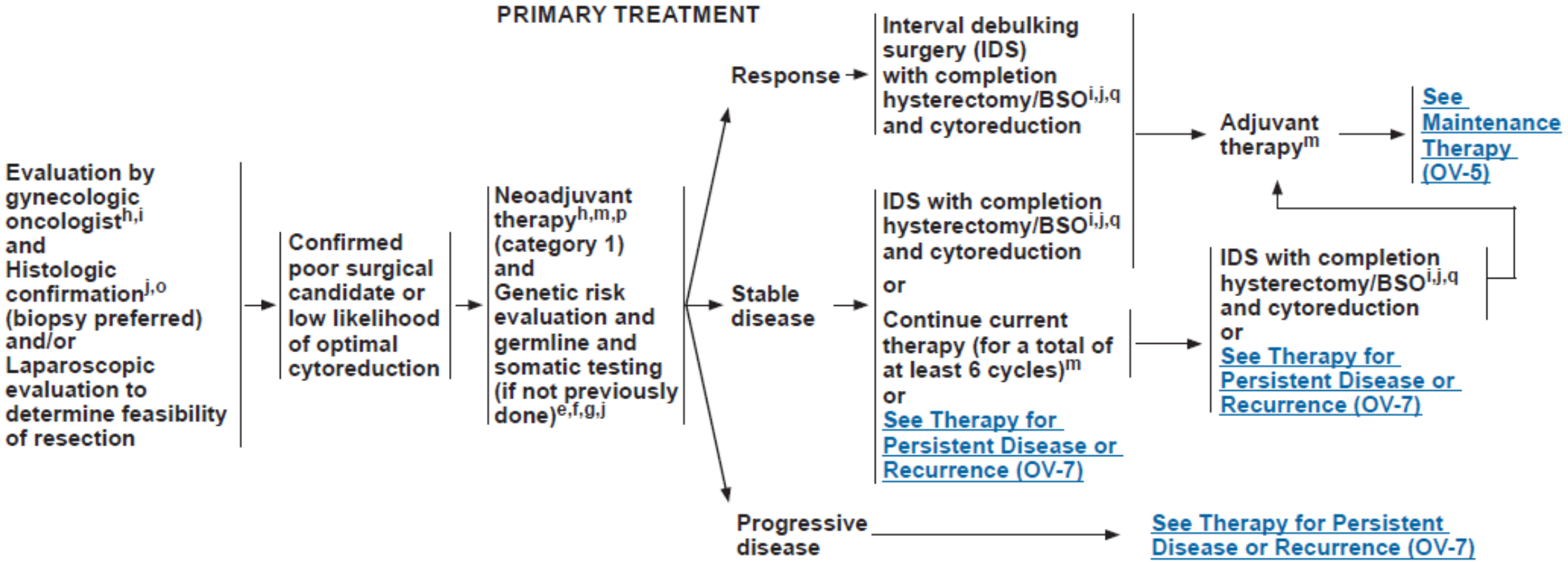
Obstet Gynecol. 2017 May;129(5):861-869.


100
80
60
40
20
0
Probability of survival (%)
P=.15
Laparotomy
Laparoscopy
0
10
20
30
40
50
60
Time since diagnosis (months)

National Comprehensive Cancer Network®

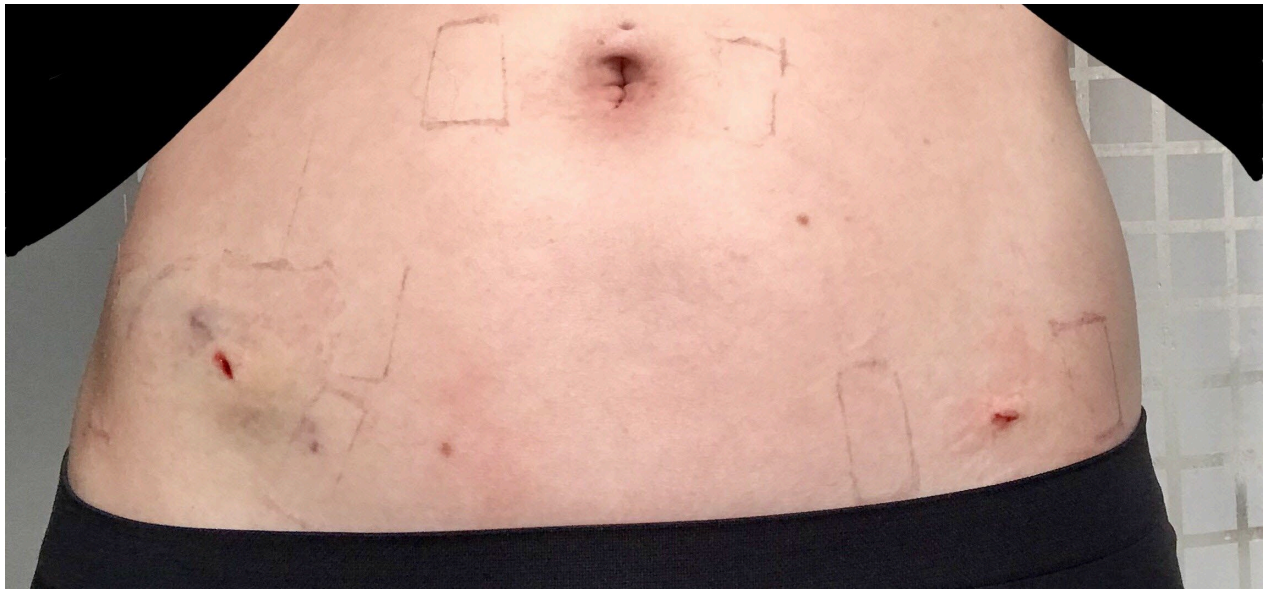
NCCN Guidelines Version 2.2022
Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer
NCCN Evidence Blocks™

POOR SURGICAL CANDIDATE OR LOW LIKELIHOOD OF OPTIMAL CYTOREDUCTION
NEOADJUVANT THERAPY



Future paradigm of stage III/IV EOC treatment

- Neoadjuvant chemotherapy
- MIS to achieve interval debulk
- Somatic & germline testing
- PARP/Olaparib maintenance



Maintenance Treatment for Recurrent Ovarian Carcinoma – Evidence Supporting the Efficacy and Safety of PARP Inhibitors

Robert L Coleman[1] and Jonathan A Ledermann[2]

1. Department of Gynecologic Oncology and Reproductive Medicine, University of Texas MD Anderson Cancer Center, Houston, Texas, USA;
2. UCL Cancer Institute and University College London Hospitals, London, UK

DOI: https://doi.org/10.17925/EOH.2019.15.1.29

While recent advances in treatment mean that women with ovarian cancer are living longer, many eventually experience disease relapse highlighting the need for new treatments that can extend progression-free survival (PFS). The PARP inhibitors olaparib, niraparib and rucaparib have been approved by the US Food and Drug Administration and the European Commission and are currently available for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy. Here, we review the efficacy and safety data from the key clinical trials supporting the approvals for these treatments as second-line maintenance therapies, including Study 19, SOLO2/ENGOT-OV21 (olaparib), NOVA/ENGOT-OV16 (niraparib) and ARIEL3 (rucaparib). Across trials, PFS was improved with PARP inhibitor maintenance treatment versus placebo in patients with a *BRCA* mutation. However, evidence from some of the trials shows that a wider group of patients can benefit from PARP inhibitor maintenance treatment including those with or without homologous recombination deficient tumours. The safety profile for olaparib, niraparib and rucaparib was generally similar across trials with haematological and gastrointestinal adverse events and fatigue/asthenia being the most common. As evidenced by the significant improvements in PFS and manageable safety profiles in these trials, PARP inhibitors represent a new standard of care for recurrent ovarian cancer following

- 3 different PARP inhibitors
- Germline/somatic BRCA1/2
- Progression-free survival
- HRs ranging 0.20-0.27

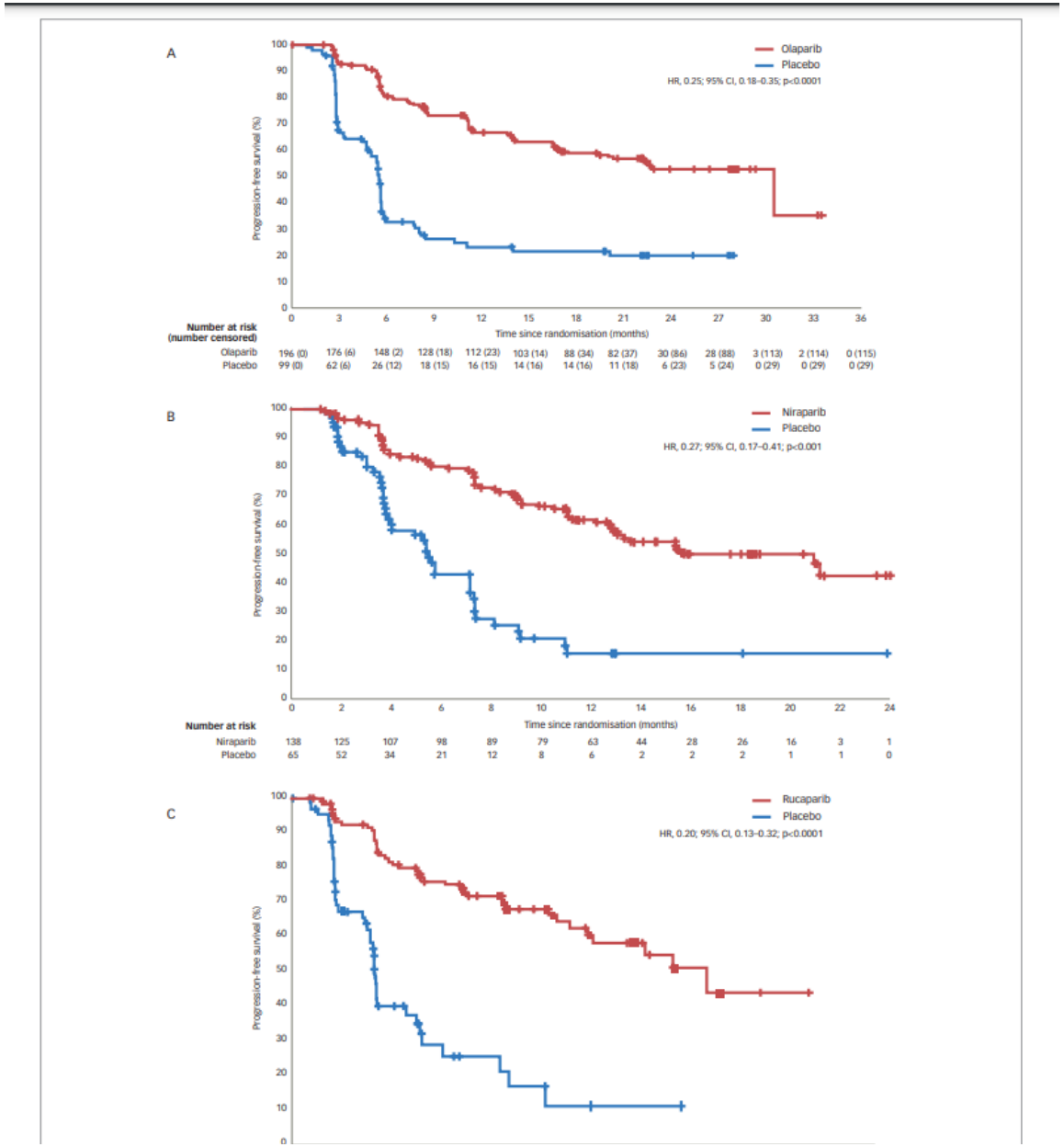
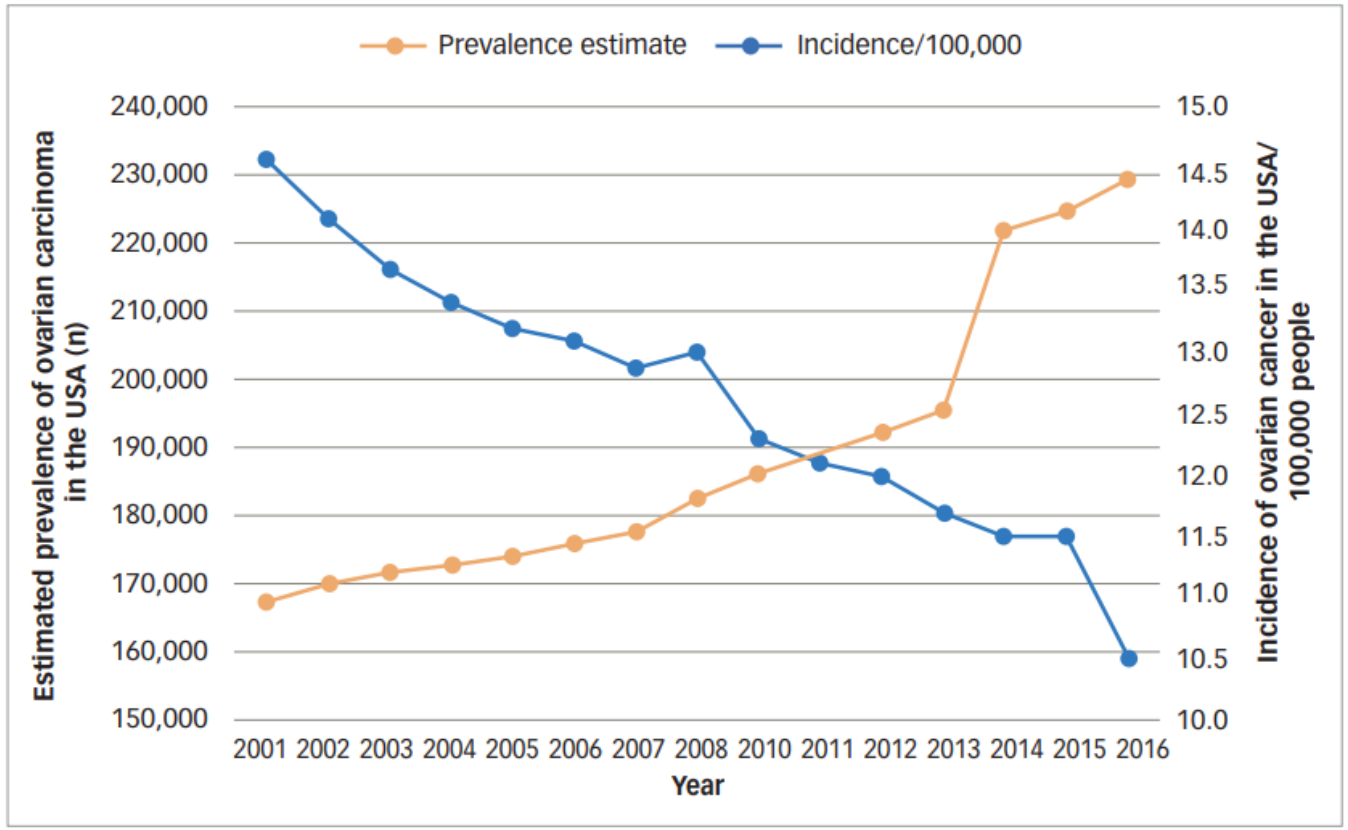


Figure 1: Estimated prevalence and incidence of ovarian cancer in the USA from 2001–2016



Source: National Cancer Institute Surveillance, Epidemiology and End Results Program (SEER) Cancer Statistics Review (CSR) 1975–2015 – Ovary Section and archival CSRs from 2001–2014.[2,4]

THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER