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## Pathologic Findings at Risk-Reducing Salpingo-Oophorectomy: Primary Results From Gynecologic Oncology Group Trial GOG-0199

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### ABSTRACT

#### Purpose

Risk-reducing salpingo-oophorectomy (RRSO) lowers mortality from ovarian/tubal and breast cancers among *BRCA1/2* mutation carriers. Uncertainties persist regarding potential benefits of RRSO among high-risk noncarriers, optimal surgical age, and anatomic origin of clinically occult cancers detected at surgery. To address these topics, we analyzed surgical treatment arm results from Gynecologic Oncology Group Protocol-0199 (GOG-0199), the National Ovarian Cancer Prevention and Early Detection Study.

#### Participants and Methods

This analysis included asymptomatic high-risk women age  $\geq 30$  years who elected RRSO at enrollment. Women provided risk factor data and underwent preoperative cancer antigen 125 (CA-125) serum testing and transvaginal ultrasound (TVU). RRSO specimens were processed according to a standardized tissue processing protocol and underwent central pathology panel review. Research-based *BRCA1/2* mutation testing was performed when a participant's mutation status was unknown at enrollment. Relationships between participant characteristics and diagnostic findings were assessed using univariable statistics and multivariable logistic regression.

#### Results

Invasive or intraepithelial ovarian/tubal/peritoneal neoplasms were detected in 25 (2.6%) of 966 RRSOs (*BRCA1* mutation carriers, 4.6%; *BRCA2* carriers, 3.5%; and noncarriers, 0.5%;  $P < .001$ ). In multivariable models, positive *BRCA1/2* mutation status ( $P = .0056$ ), postmenopausal status ( $P = .0023$ ), and abnormal CA-125 levels and/or TVU examinations ( $P < .001$ ) were associated with detection of clinically occult neoplasms at RRSO. For 387 women with negative *BRCA1/2* mutation testing and normal CA-125 levels, findings at RRSO were benign.

#### Conclusion

Clinically occult cancer was detected among 2.6% of high-risk women undergoing RRSO. *BRCA1/2* mutation, postmenopausal status, and abnormal preoperative CA-125 and/or TVU were associated with cancer detection at RRSO. These data can inform management decisions among women at high risk of ovarian/tubal cancer.

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### INTRODUCTION

Risk-reducing salpingo-oophorectomy (RRSO) reduces number of deaths resulting from ovarian/tubal and breast cancers among carriers of deleterious *BRCA1/2* mutations and thus has become a preferred management strategy for these women.<sup>1-3</sup> Although oral contraceptive use and tubal ligation reduce the risk of ovarian/tubal neoplasms, level of protection is lower than that achieved with RRSO, and breast cancer risk is not reduced.<sup>4-7</sup> The effectiveness of screening in reduc-

ing mortality attributable to these cancers remains unproven. Annual concurrent cancer antigen 125 (CA-125) serum testing and transvaginal ultrasound (TVU) in the Prostate, Lung, Colorectal and Ovarian trial did not reduce ovarian/tubal cancer mortality.<sup>8</sup> Preliminary results from the UK Collaborative Trial of Ovarian Cancer Screening, which targeted similar women, reported potentially better results using algorithm-based CA-125 testing with secondary TVU examination<sup>9</sup>; final results are pending, and data from high-risk women are just emerging.<sup>10</sup> Thus, determining which women

benefit most from RRSO and the age at which surgery provides maximum protection with minimum adverse effects from hormone deprivation remains critical.<sup>11-13</sup>

Clinical acceptance of RRSO has provided pathologists with opportunities to study small ovarian/tubal neoplasms, prompting new insights into their pathogenesis. We now know that many high-grade serous cancers, the numerically predominant and most lethal subtype of ovarian/tubal cancer, arise from the fallopian tube fimbria, not the ovary, as previously supposed.<sup>14-19</sup> This has prompted discussions of a two-stage prevention strategy in which salpingectomy with ovarian retention would be performed in younger women, followed by oophorectomy at a later time.<sup>20</sup> However, this approach remains investigational.<sup>21-23</sup>

The reported frequency of clinically occult neoplasms in RRSO varies widely, reflecting differences in study populations, pathology processing, and diagnosis.<sup>2,16,24-55</sup> Prior reports are characterized by small size, incomplete risk factor information (eg, missing *BRCA1/2* data), variable preoperative clinical testing assessment, differences in symptomatic disease exclusion criteria, and retrospective analysis of nonstandardized pathology diagnoses. The prevalence of occult neoplasms at RRSO in six prospective studies<sup>34,40,47-49,55</sup> averages as follows: all *BRCA*-positive participants, 3.7%; *BRCA1* positive, 4.4%; *BRCA2* positive, 2.0%; and high-risk/mutation-negative/unknown status, 0.5% (Data Supplement). The literature includes only approximately 150 reports of occult cancers at RRSO, most from retrospective studies. Accordingly, we now report results from the surgical intervention arm of Gynecologic Oncology Group (GOG) Protocol-0199 (GOG-0199), the Prospective Study of Risk-Reducing Salpingo-Oophorectomy and Longitudinal CA-125 Screening Among Women at Increased Genetic Risk of Ovarian Cancer (also known as National Ovarian Cancer Prevention and Early Detection Study).<sup>56</sup> GOG-0199 is a nonrandomized multicenter trial of women at high-risk of ovarian/tubal neoplasia comparing health outcomes among women who chose between RRSO or screening (CA-125- and TVU-based testing, according to risk of ovarian cancer algorithm).<sup>57</sup>

PARTICIPANTS AND METHODS

Participants

Eligible participants included women age ≥ 30 years who were at high risk of developing ovarian/tubal/primary peritoneal cancer based on being *BRCA1/2* mutation positive or having a strong family history (specified elsewhere<sup>56</sup>), not clinically suspected of having a gynecologic cancer, and being managed with preventive rather than therapeutic intent.<sup>56</sup> Given the low screening test sensitivity and specificity of CA-125 and TVU, normal results for these tests were not required for eligibility. Candidate participants with abnormalities considered insufficient to merit a workup for cancer were included. At enrollment, participants elected immediate RRSO or screening, with the option to cross over to the RRSO arm postenrollment, either electively or for indications. From June 2003 to November 2006, 1,575 and 1,030 women were enrolled onto the screening and RRSO arms, respectively; 28 had unconfirmed eligibility, and 36 not undergoing RRSO per protocol were excluded, leaving 966 eligible surgical participants (Fig 1). Protocol NCT-00049049 was approved by institutional review boards at the National Cancer Institute, GOG, and 151 GOG institutions (United States and Australia).

Baseline Study Procedures

Participants completed ovarian/tubal cancer risk factor, medical history, quality-of-life, and medical decision-making questionnaires; donated blood for serum and DNA; and underwent CA-125 testing and TVU before RRSO. Mutation status was known for 962 (99.6%) of 966 participants, from clinical and research-based mutation testing.<sup>56</sup> Women electing RRSO underwent surgery within 90 days of enrollment, with intraoperative pelvic organ visual inspection, peritoneal lavage cytology, and total removal of both ovaries and fallopian tubes. Hysterectomy was performed electively, per patient and physician discretion.

Pathology Processing and Panel Review

The protocol stipulated that ovaries and fallopian tubes be sectioned at 2- to 3-mm intervals and entirely submitted for histologic examination (reported as done in 85% of pathology reports). Medians of 16, 17, and 15 slides (each potentially containing multiple sections) per RRSO were submitted for *BRCA1* mutation carriers, *BRCA2* mutation carriers, and noncarriers, respectively. Centers enrolling ≤ 20 participants submitted a median of 15 slides per RRSO versus 17 for higher enrolling centers.

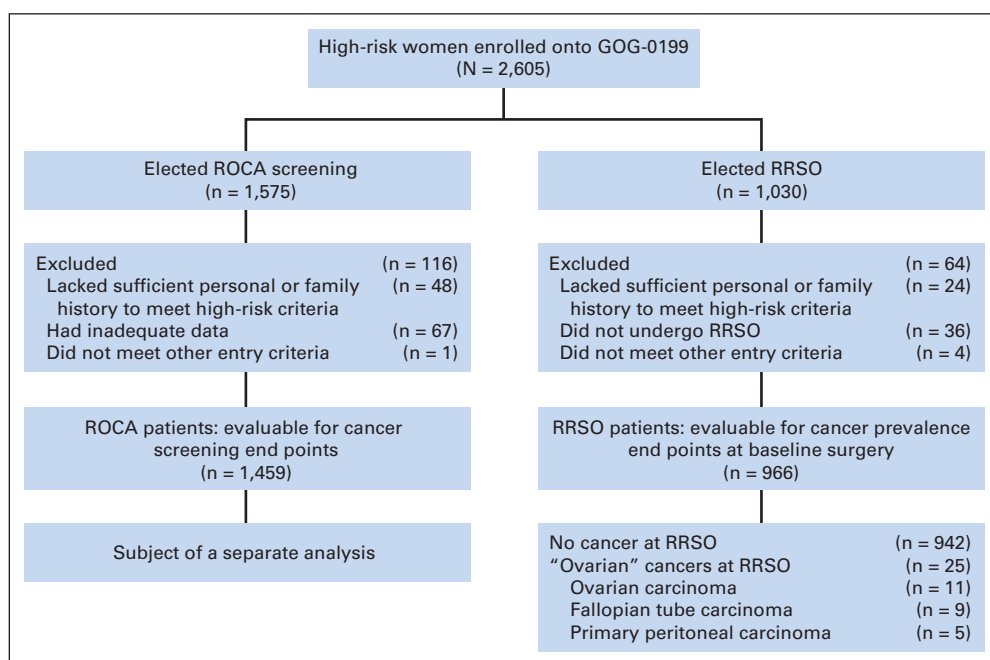


Fig 1. CONSORT diagram for GOG (Gynecologic Oncology Group) 0199, the National Ovarian Cancer Prevention and Early Detection Study. ROCA, risk of ovarian cancer algorithm; RRSO, risk-reducing salpingo-oophorectomy.

Hematoxylin and eosin–stained surgical pathology slides from 957 (99.1%) RRSOs and cytopathology slides of peritoneal washes from 881 (91.2%) were initially reviewed (M.E.S.) to identify cancer and determine its primary site, histologic subtype, grade, and extent. RRSOs showing serous tubal intraepithelial carcinoma (STIC) associated with invasive cancer were designated as primary fallopian tube cancers; primary sites of the remaining cancers were assigned based on distribution and extent of tumor deposits. Grading and staging were performed according to the International Federation of Gynecology and Obstetrics classification. Cases initially classified as invasive cancer, STIC, or tubal atypia of any severity were reviewed independently by a second pathologist (O.B.I.) and then jointly reviewed to resolve discrepancies. Final diagnoses were assigned in a consensus review conducted by three pathologists (M.E.S., O.B.I., B.M.R.), masked to prior diagnoses. Our analysis is limited to cases with consensus diagnosis of STIC or invasive cancer.

**Statistical Methods**

Frequencies and percentages with 95% CIs of invasive cancer and STIC were defined overall and by specific participant characteristics: pertinent medical history, including race, age, menopausal status, family history of breast and ovarian cancer, *BRCA1/2* mutation status, personal history of breast cancer, use of oral contraceptives or menopausal hormones, parity, tamoxifen use, and preoperative testing, including CA-125 levels (upper normal: premenopausal, 50 U/mL; postmenopausal, 35 U/mL), TVU results, and test combinations.<sup>58</sup> The primary outcome for this analysis was STIC or invasive ovarian/tubal/peritoneal cancer, referred to herein as ovarian/tubal neoplasm. Single-factor associations between categorical variables and frequency of ovarian/tubal neoplasms were assessed with Fisher’s exact tests; associations for age as a continuous variable were evaluated using nonparametric Kruskal-Wallis tests. To assess factors independently associated with pathologic findings, we performed multivariable logistic regression; the outcome variable was detection of ovarian/tubal neoplasm, and explanatory variables included specific factors that were included in the final model, using stepwise forward selection at levels of *P* < .05.

**RESULTS**

**Prevalence of Invasive Cancer and STIC by Participant Characteristics**

Characteristics among *BRCA1* mutation carriers, *BRCA2* mutation carriers, and noncarriers were identical for all but three factors: ovarian cancer family history (*BRCA1* carriers, 55.0%; *BRCA2* carriers, 33.2%; and noncarriers, 57.7%; *P* < .001), menopausal hormone use (*BRCA1* carriers, 61.3%; *BRCA2* carriers, 51.6%; and noncarriers, 44.2%; *P* < .001), and tamoxifen use (*BRCA1* carriers, 17.9%; *BRCA2* carriers, 27.4%; and noncarriers, 32.8%; *P* = .001).

Among 966 participants, 25 (2.6%; 95% CI, 1.6% to 3.6%) were diagnosed with ovarian/tubal neoplasms, including 15 of 326 *BRCA1* mutation carriers (4.6%; 95% CI, 2.3% to 6.9%), eight of 231 *BRCA2* carriers (3.5%; 95% CI, 1.1% to 5.8%), and two of 403 noncarriers (0.5%; 95% CI, -0.2% to 1.2%; *P* < .001). These 25 participant cases included four STICs (*BRCA1*, *n* = 2; *BRCA2*, *n* = 2).

Women with ovarian/tubal neoplasms were older than those with benign pathology (age 52.7 v 47.1 years; *P* < .001; Table 1). Neoplasms were detected among 4.5% of postmenopausal women versus 1.2% of premenopausal women (*P* = .003). Past tamoxifen use, but not personal history of breast cancer, was marginally associated with ovarian/tubal neoplasm (*P* = .04). Ovarian/tubal neoplasms were found among 10.6% of women with abnormal TVU and/or elevated CA-125 level versus 1.6% of those with both tests normal, a difference almost entirely attributable to elevated CA-125 results. Neoplasms were detected among seven (26.9%) of 26 women with abnormal CA-125 tests only, one (1.3%) of 77 women with abnor-

**Table 1.** Characteristics of Women Undergoing RRSO in GOG-0199: National Ovarian Cancer Prevention and Early Detection Study (N = 966)\*

Characteristic	Negative RRSO (n = 941)		Invasive Cancer/STIC (n = 25)		P
	No.	%	No.	%	
Baseline CA-125/TVU					< .001
Normal/normal	805	88.6	13	54.0	
Abnormal/normal	19	2.1	7	29.2	
Normal/abnormal	76	8.4	1	4.2	
Abnormal/abnormal	9	1.0	3	12.5	
Age, years					< .001
Median		47.1		52.7	
IQR		41.5-53.4		47.9-58.3	
Menopausal status					.003
Premenopausal	559	59.4	7	28.0	
Postmenopausal	382	40.6	18	72.0	
Race					NS
White	892	95.3	24	96.0	
Black	32	3.4	1	4.0	
Other	12	1.3	0	0.0	
Nulliparous					NS
No	700	85.0	15	71.4	
Yes	124	15.0	6	28.6	
Family history					
Breast cancer					NS
No	153	16.8	1	4.4	
Yes	755	83.2	22	95.6	
Ovarian cancer					NS
No	444	49.0	13	56.5	
Yes	463	51.0	10	43.5	
<i>BRCA</i> mutation status†					< .001
Noncarrier	401	42.3	2	8.0	
<i>BRCA1</i> positive	311	33.3	15	60.0	
<i>BRCA2</i> positive	223	23.8	8	32.0	
Double positive	2	0.2	0	0.0	
OC use					NS
Current	51	5.4	0	0.0	
Former	630	67.2	15	60.0	
Never	257	27.4	10	40.0	
Menopausal hormone use					NS
Current	165	18.2	1	4.4	
Former	269	29.7	11	47.8	
Never	471	52.0	11	47.8	
Personal history of breast cancer					NS
No	421	44.7	10	40.0	
Yes	520	55.3	15	60.0	
Tamoxifen use					.04
Current	119	13.2	0	0.0	
Former	120	13.3	6	26.1	
Never	666	73.6	17	73.9	

Abbreviations: CA-125, cancer antigen 125; GOG, Gynecologic Oncology Group; IQR, interquartile range; NS, not significant; OC, oral contraceptive; RRSO, risk-reducing salpingo-oophorectomy; STIC, serous tubal intraepithelial carcinoma; TVU, transvaginal ultrasound.

\*Numbers might not add up to total of 966 because of missing values.

†Two participants with both *BRCA1* and *BRCA2* mutations were excluded from this analysis.

mal TVU only, three (25.0%) of 12 women with both tests abnormal, and 13 (1.6%) of 818 women with normal results for both tests (*P* < .001; Table 1). Among *BRCA* mutation–negative women, 15 (3.7%) of 402 had abnormal CA-125 levels; neoplasms were not

observed among 387 mutation-negative participants with normal baseline CA-125.

CA-125 levels > 100 U/mL were recorded for 14 women (one with a suspicious TVU), including seven with cancers detected at RRSO (ovarian, n = 4; peritoneal, n = 2; and tubal primary, n = 1). Twelve cancers (BRCA1, n = 8; BRCA2, n = 2; and noncarriers, n = 2) occurred among the 116 women with a TVU abnormality and/or CA-125 elevation. After excluding these 116 participants, the remaining 13 prevalent cancers occurred among 496 BRCA1/2 mutation carriers versus none of the 350 noncarriers.

In multivariable models, postmenopausal status (odds ratio [OR], 4.8; 95% CI, 1.8 to 13.2), positive BRCA1/2 mutation test (OR, 8.3; 95% CI, 1.9 to 37.0), and abnormal CA-125 and/or TVU results (OR, 13.8; 95% CI, 5.2 to 36.3) were independently associated with ovarian/tubal neoplasm at RRSO. In models excluding 27 women with suspicious TVUs and/or CA-125 levels > 100 U/mL, factors

associated with neoplasms included: BRCA1/2 mutation (OR, 11.3; 95% CI, 1.4 to 87.9), abnormal baseline test (OR, 6.5; 95% CI, 1.8 to 24.3), and menopausal status (OR, 4.0; 95% CI, 1.2 to 13.3). Cancers were not observed among noncarriers with normal baseline tests; among carriers, older age and postmenopausal status were associated with a similar level of minimal risk (OR, 1.1; 95% CI, 1.0 to 1.1).

**Clinical Characteristics of Invasive Cancers and STICs in GOG-0199**

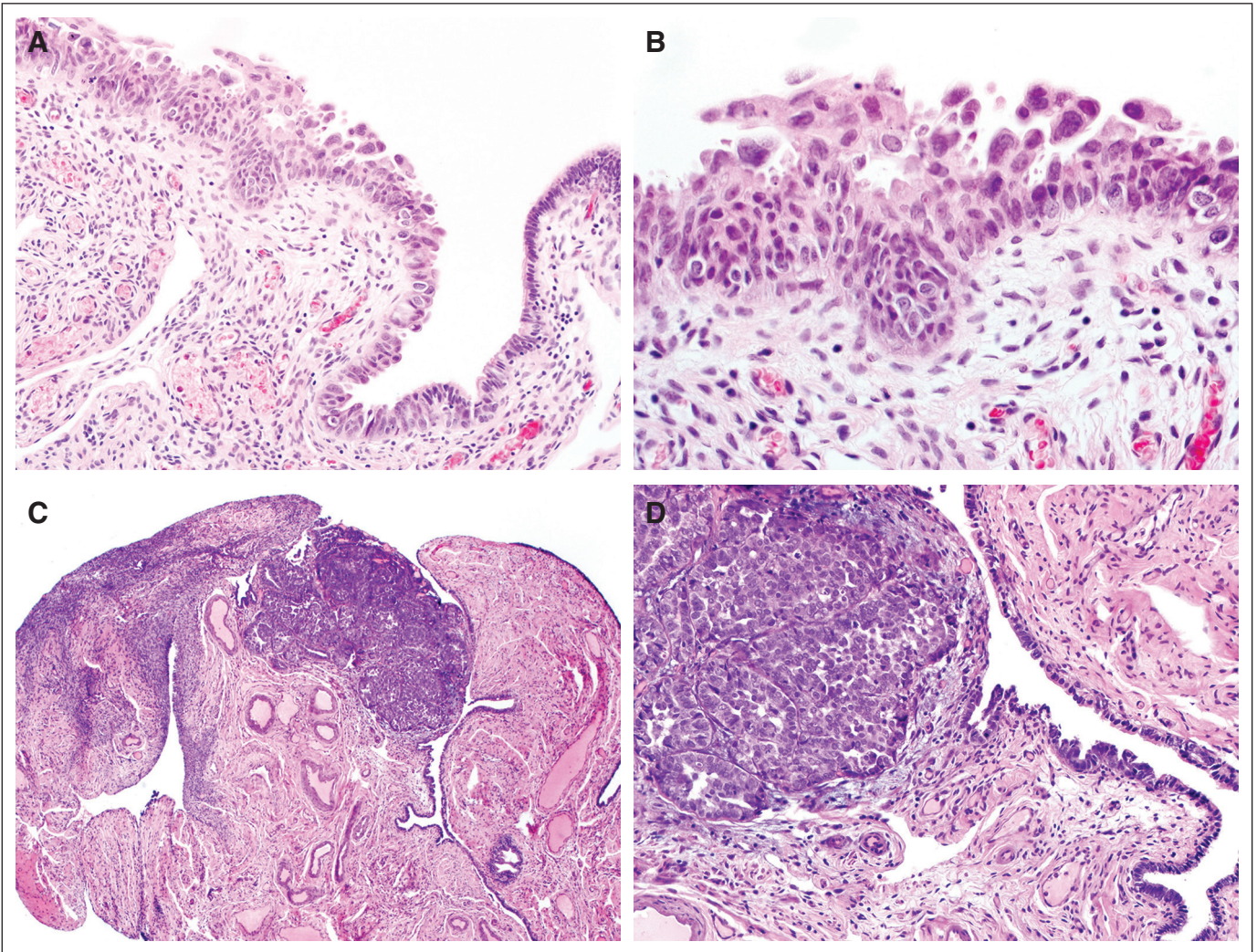
The neoplasms detected at RRSO were classified as ovarian (n = 10), tubal (n = 10), and primary peritoneal (n = 5). Among 21 invasive cancers, 13 were serous, two were endometrioid, and six were mixed/unclassifiable histologic type (Table 2). Fourteen neoplasms were stages 0 to II, including five ovarian and nine tubal primaries (four STICs), of which 11 showed minimal disease volumes (≤ 1 cm), and three demonstrated macroscopic ovarian cancer (Fig 2). Women

**Table 2.** Characteristics of Cancers Detected at RRSO in GOG-0199: National Ovarian Cancer Prevention and Early Detection Study

Histology	Age (years)	Cytology	Stage*	CA-125 (U/mL)	Tumor Volume
<b>Ovary</b>					
<i>BRCA1</i>					
Serous adenocarcinoma	44	Positive	IIIC	110	Multiple ovarian and peritoneal nodules
	44	Positive	IIIC	158	8-cm mass in right ovary
	46	Negative	IIA	28	2.7-cm mass in right ovary
	58	Missing	IIIC	1,128	6-cm friable mass in left ovary; 3.8-cm mass in right ovary
Adenocarcinoma with squamous differentiation	46	Positive	IIIB	12	1.1-cm nodule in right ovary
Endometrioid adenocarcinoma	50	Negative	IB	24	Microscopic foci in both ovaries
Mixed epithelial adenocarcinoma	52	Positive	IIIC	336	Multiple omental implants and nodules
<i>BRCA2</i>					
Serous adenocarcinoma	54	Positive	IC	11	1-mm focus in left and right ovaries
	55	Negative	IC	12	2.2-cm nodule in right ovary; 1.5-cm nodule in left ovary identified on sectioning
Endometrioid adenocarcinoma	51	Negative	IB	66	2-cm lobulated mass in left ovary identified on sectioning
<b>Fallopian tube</b>					
<i>BRCA1</i>					
Serous adenocarcinoma	42	Positive	IIC	11	0.5-cm arising from fimbriated end of right FT; 0.25-cm focus on surface of right ovary
	61	Positive	IIIC	974	5-cm mass in left FT
Adenocarcinoma	59	Negative	IA	16	1-cm mass in fimbriated end of left FT
Serous tubal intraepithelial carcinoma	48	Negative	0	20	Microscopic focus
	58	Negative	0	14	Microscopic focus
<i>BRCA2</i>					
Serous adenocarcinoma	71	Negative	IA	20	Microscopic focus in left FT
	55	Positive	IIC	ND	Microscopic foci in ovaries and left FT
Serous tubal intraepithelial carcinoma	56	Negative	0	8	Microscopic focus
	55	Negative	0	11	Microscopic focus
<i>BRCA mutation negative</i>					
Adenocarcinoma	73	Negative	IA	67	Microscopic focus in left FT
<b>Primary peritoneal</b>					
<i>BRCA1</i>					
Serous adenocarcinoma	51	Positive	IIIC	1,064	Numerous omental masses
	60	Positive	IIIC	20	Microscopic omental nodules and intraluminal papillary adenocarcinoma
Adenocarcinoma	47	Positive	III	72	1.2-cm cul-de-sac nodule
<i>BRCA2</i>					
Carcinoma NOS	52	Positive	III	6	Microscopic focus in left ovary
<i>BRCA mutation negative</i>					
Serous adenocarcinoma	50	Positive	III	196	Microscopic foci in both ovaries

Abbreviations: FT, fallopian tube; ND, not done; NOS, not otherwise specified; RRSO, risk-reducing salpingo-oophorectomy.

\*Information on complete staging was available for only one of 14 early-staged participant cases; 2012 version of International Federation of Gynecology and Obstetrics staging system was used.



**Fig 2.** Neoplastic lesions arising in fallopian tube. (A) Low-power ( $\times 10$  magnification) photomicrograph showing transition from benign fallopian tube epithelium composed of uniform columnar cells (far right) to serous tubal intraepithelial cancer. (B) High-power ( $\times 20$  magnification) view of (A), demonstrating malignant-appearing cells with pleomorphic nuclei. (C) Nodule of invasive high-grade serous cancer with suggested origin from fallopian tube epithelium ( $\times 10$  magnification). (D) High-power ( $\times 20$  magnification) view of (C), showing solid sheets of tumor cells with suggestion of irregular gland formation; right side of image shows benign fallopian tube epithelium.

with stage I cancers presented a median CA-125 level of 20 U/mL (range, 11 to 67 U/mL) versus 196 U/mL (range, 12 to 1,128 U/mL) among those with stage III cancers. All cases of STIC occurred among mutation carriers with normal CA-125 levels (range, 8 to 20 U/mL). Peritoneal washes were positive in 14 (1.6%) of 881 cases of invasive cancer, including 13 ovarian/tubal neoplasms and one endometrial cancer (Table 2; Appendix Table A1, online only). All participant cases with positive washes had cancer in surgical pathology specimens.

Among 515 women who underwent elective hysterectomy, six (1.2%) harbored endometrial cancer, including two cases each of uterine endometrioid and mucinous cancers among noncarriers and two serous cancers among *BRCA1* mutation carriers (Appendix Table A1, online only).

## DISCUSSION

Our results demonstrated ovarian/tubal neoplasms in 2.6% of RRSOs (*BRCA1* mutation carriers, 4.6%; *BRCA2* mutation carriers, 3.5%;

and high-risk noncarriers, 0.5%). This frequency is similar to reported results, including a recent prospective study where the prevalence of ovarian/tubal/peritoneal cancers was 4.2% among *BRCA1* mutation carriers<sup>55</sup> (Data Supplement). Use of more sensitive sectioning protocols (longitudinal and transverse sectioning), combined with growing diagnostic acumen (immunohistochemistry, focus on fimbriae), suggests that our estimates of STIC and early tubal neoplasia may prove low. Nonetheless, given the size and breadth of ascertainment in GOG-0199, our estimates of prevalent neoplastic lesions at RRSO provide state-of-the-science evidence for decision making and management.

Although women with suspicious symptoms were considered ineligible, we cannot confirm strict protocol adherence to this requirement. Furthermore, abnormal or worrisome preoperative screening tests were not considered exclusions, because of the nonspecificity of positive testing in the general population.<sup>8</sup> Overall, 9.6% of women had abnormal CA-125 levels, TVU, or both, including 50% of women with invasive ovarian/tubal cancer. Three of six women with invasive

tubal cancer had abnormalities in CA-125 levels and/or TVU, whereas all four women with STIC had normal results, suggesting that RRSO offers protection that would be unachievable by screening high-risk women. In addition, we identified two groups of women in whom neoplasms were not found: noncarriers with normal CA-125 levels and high-risk women age < 42 years.

High CA-125 concentrations have been linked to detection of cancer or dysplasia in prophylactic or diagnostic RRSO.<sup>59</sup> In our analysis, seven of 14 women with CA-125 levels  $\geq$  100 U/mL had cancer (ovarian,  $n = 4$ ; peritoneal,  $n = 2$ ; tubal,  $n = 1$ ), only one of whom had an abnormal TVU, which may partly explain why these women were considered eligible for enrollment.

In this study, neoplasm prevalence was higher among older postmenopausal women; none of the women with neoplasms was age < 42 years, consistent with prior data linking increasing age and risk.<sup>34</sup> Although younger *BRCA1* carriers are at markedly elevated relative risk of ovarian/tubal cancer, their absolute risk up to age 40 years is approximately  $\leq$  3%.<sup>60,61</sup> Nonetheless, *BRCA*-related ovarian/tubal neoplasms may occur at younger ages, particularly among *BRCA1* mutation carriers. A recent report<sup>55</sup> found that the estimated risk of ovarian/tubal cancer before or at the time of RRSO among *BRCA1* mutation carriers was 4% if surgery was delayed until age 40 years. The absence of neoplasms among the youngest GOG-0199 participants reflects the infrequency of such cases, the number of younger women and the number of *BRCA1* mutation carriers in this study, and the probability that early-onset cancers may present symptomatically before ages at which RRSO is considered. Thus, in accordance with standards of care, many *BRCA1/2* mutation carriers opt for early RRSO, prior to age-related increases in risk.<sup>62</sup> Among noncarriers in their 40s, whose ovarian cancer risk is lower but poorly defined, development of chronic morbidity and mortality secondary to surgical menopause complicates this choice. Developing age-specific risk/benefit models related to RRSO would be clinically useful.<sup>11-13</sup> In GOG-0199, microscopic neoplasms were found within the tubes and ovaries, supporting prior recommendations to entirely submit these tissues for histologic examination.<sup>27,63,64</sup> Cytopathologic review of peritoneal cytology did not affect detection of malignancy.

Eleven women in this trial presented with minimal disease, including four with STICs, four with small invasive tubal cancers, two with minimal ovarian involvement, and one with involvement of both ovaries and the left fallopian tube, consistent with the view that the fallopian tube is an important source of high-grade serous cancers.<sup>14-17</sup> As performance of RRSO with meticulous pathologic assessment has become more common, detection of early neoplastic lesions has risen, posing new challenges to optimal staging and management of women with minimal or noninvasive disease. In GOG-0199, most large invasive cancers produced bulky ovarian disease and were therefore classified as primary ovarian tumors when STIC was not identified, which may have resulted in underestimation of the number of tubal primaries.<sup>2,24-33,35-38,41,60</sup>

Bilateral salpingectomy with deferred oophorectomy has been proposed as a temporizing prevention measure for high-risk individuals, enabling premenopausal women to postpone oophorectomy and maintain ovarian function for a longer time period.<sup>20</sup> Developing sensitive methods to exclude occult neoplastic lesions in retained ovaries would strengthen the promise of this approach, as would defining precisely the age-specific risks of ovarian, fallopian tube, and breast cancers and chronic diseases secondary to hormone depriva-

tion among women with different risk factor profiles.<sup>18,65-66</sup> Although developing a unified pathogenetic model for high-grade serous ovarian/tubal neoplasia is appealing, it is notable that only two cancers were found among 403 high-risk noncarriers in GOG-0199, underscoring the need to determine whether managing these women similarly to *BRCA1/2* mutation carriers—as is currently done—is optimal. Other data also suggest that risk of ovarian/tubal cancer in *BRCA* mutation-negative familial breast cancer families is lower than among mutation-positive women.<sup>67</sup> STIC remains poorly described among noncarriers, particularly without concurrent invasive fallopian tube cancer.<sup>18</sup>

Six women had endometrial cancer at RRSO, including two serous cancers (0.6%) in 326 *BRCA1* mutation carriers and four (1.0%) in 403 noncarriers. Serous endometrial cancer has been linked to prior breast cancer, tamoxifen use, and, inconsistently, with *BRCA1* mutation.<sup>68-70</sup> Endometrial serous cancers may be associated with lesions resembling STIC, perhaps representing independent primaries or intramucosal spread from a single primary tumor.<sup>71</sup> Given these data, thorough microscopic endometrial examination is warranted when hysterectomy is performed with RRSO.

Strengths of this study include its large sample size, prospective design, recruitment from diverse practice settings, inclusion of mutation-negative/strong family history-positive women, comprehensive assessment of risk factors and *BRCA1/2* mutation status, implementation of a standardized tissue processing protocol, and central pathology review. To our knowledge, this is the largest study to date in which the *BRCA* mutation status of all participants was known, all surgical pathology material was handled via a predefined protocol, and a rigorous, explicit effort was made to exclude symptomatic women from study entry. Consequently, our results can be generalized with confidence to different groups of women and practice settings.

Although GOG-0199 was designed to enroll asymptomatic high-risk women, nearly 12% of participants had abnormal baseline tests, raising concerns about whether these women were vaguely symptomatic or encouraged to undergo RRSO on that basis. However, compared with the GOG-0199 screening arm, women in the surgical arm did not have a significantly higher frequency of abnormal screening tests (TVU and/or CA-125; 12.4%  $\nu$  10.9%) or abnormal TVU (9.6%  $\nu$  8.9%), but they did have a slightly higher frequency of elevated CA-125 levels (surgical arm, 4.0%  $\nu$  screening arm, 2.4%;  $P = .03$ ). These data argue against a strong referral bias toward RRSO. These factors may have contributed to overestimation of the frequency of asymptomatic prevalent cancer; however, this likely represents real-world practice. Conversely, it is possible that some fallopian tubes and ovaries were not entirely submitted for microscopy, despite that protocol requirement; this may have led to underestimation of neoplasm prevalence. Incomplete ascertainment of STIC end points is impossible to eliminate, because even sectioning-blocked tissues at 2- to 3-mm thickness may miss focal lesions without serial sectioning. Furthermore, some GOG-0199 participant cases may have been upstaged after RRSO. Finally, GOG-0199 was not designed to assess the risk-reducing value of hysterectomy, which was chosen electively by participants and physicians, and indications for that procedure were not collected.

In summary, this nonrandomized prospective clinical trial found that 2.6% of women undergoing RRSO were diagnosed with ovarian/tubal neoplasms, including 4.6% of *BRCA1* mutation carriers, 3.5% of *BRCA2* mutation carriers, and 0.5% of noncarriers. Overall, 56% of

women with ovarian/tubal neoplasia had STIC or stage I or II invasive cancer, suggesting an improved prognosis compared with symptomatic presentation. Older, postmenopausal carriers of *BRCA1/2* mutations who presented with abnormal CA-125 serum levels or TVU were more likely to have invasive neoplasms at RRSO, whereas women lacking these features were at lower risk of neoplastic findings, especially if mutation negative. Our data suggest that assessing factors associated with cancer at RRSO may enable improved, patient-specific management decisions, which reflect complex considerations related to cancer prevention, risks of non-neoplastic disease, and quality of life.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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#### REFERENCES

1. Rebbeck TR, Kauff ND, Domchek SM: Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in *BRCA1* or *BRCA2* mutation carriers. *J Natl Cancer Inst* 101:80-87, 2009
2. Kauff ND, Satagopan JM, Robson ME, et al: Risk-reducing salpingo-oophorectomy in women with a *BRCA1* or *BRCA2* mutation. *N Engl J Med* 346:1609-1615, 2002
3. Domchek SM, Friebel TM, Singer CF, et al: Association of risk-reducing surgery in *BRCA1* or *BRCA2* mutation carriers with cancer risk and mortality. *JAMA* 304:967-975, 2010
4. Cibula D, Zikan M, Dusek L, et al: Oral contraceptives and risk of ovarian and breast cancers in *BRCA* mutation carriers: A meta-analysis. *Expert Rev Anticancer Ther* 11:1197-1207, 2011
5. Beral V, Doll R, Hermon C, et al: Ovarian cancer and oral contraceptives: Collaborative reanalysis of data from 45 epidemiological studies including 23,257 women with ovarian cancer and 87,303 controls. *Lancet* 371:303-314, 2008
6. Iodice S, Barile M, Rotmensz N, et al: Oral contraceptive use and breast or ovarian cancer risk in *BRCA1/2* carriers: A meta-analysis. *Eur J Cancer* 46:2275-2284, 2010
7. Cibula D, Widschwendter M, Majek O, et al: Tubal ligation and the risk of ovarian cancer: Review and meta-analysis. *Hum Reprod Update* 17:55-67, 2011
8. Buys SS, Partridge E, Black A, et al: Effect of screening on ovarian cancer mortality: The Prostate, Lung, Colorectal and Ovarian (PLCO) cancer screening randomized controlled trial. *JAMA* 305:2295-2303, 2011
9. Menon U, Gentry-Maharaj A, Hallett R, et al: Sensitivity and specificity of multimodal and ultrasound screening for ovarian cancer, and stage distribution of detected cancers: Results of the prevalence screen of the UK Collaborative Trial of

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Ovarian Cancer Screening (UKCTOCS). *Lancet Oncol* 10:327-340, 2009

10. Rosenthal AN, Fraser L, Manchanda R, et al: Results of annual screening in phase I of the United Kingdom familial ovarian cancer screening study highlight the need for strict adherence to screening schedule. *J Clin Oncol* 31:49-57, 2013
11. McCarthy AM, Menke A, Ouyang P, et al: Bilateral oophorectomy, body mass index, and mortality in U.S. women aged 40 years and older. *Cancer Prev Res (Phila)* 5:847-854, 2012
12. Parker WH, Broder MS, Chang E, et al: Ovarian conservation at the time of hysterectomy and long-term health outcomes in the nurses' health study. *Obstet Gynecol* 113:1027-1037, 2009
13. Rocca WA, Grossardt BR, de Andrade M, et al: Survival patterns after oophorectomy in premenopausal women: A population-based cohort study. *Lancet Oncol* 7:821-828, 2006
14. Kurman RJ, Shih IeM: Molecular pathogenesis and extraovarian origin of epithelial ovarian cancer: Shifting the paradigm. *Hum Pathol* 42:918-931, 2011
15. Crum CP, McKeon FD, Xian W: The oviduct and ovarian cancer: Causality, clinical implications, and "targeted prevention". *Clin Obstet Gynecol* 55:24-35, 2012
16. Piek JM, van Diest PJ, Zweemer RP, et al: Dysplastic changes in prophylactically removed fallopian tubes of women predisposed to developing ovarian cancer. *J Pathol* 195:451-456, 2001
17. Dubeau L: The cell of origin of ovarian epithelial tumours. *Lancet Oncol* 9:1191-1197, 2008
18. Sherman ME, Guido R, Wentzensen N, et al: New views on the pathogenesis of high-grade pelvic serous carcinoma with suggestions for advancing future research. *Gynecol Oncol* 127:645-650, 2012
19. Przybycin CG, Kurman RJ, Ronnett BM, et al: Are all pelvic (nonuterine) serous carcinomas of tubal origin? *Am J Surg Pathol* 34:1407-1416, 2010
20. Greene MH, Mai PL, Schwartz PE: Does bilateral salpingectomy with ovarian retention warrant consideration as a temporary bridge to risk-reducing bilateral oophorectomy in *BRCA1/2*

mutation carriers? *Am J Obstet Gynecol* 204:19.e1-19.e6, 2011

21. Kotsopoulos IC, Tsapanos VS: Patient groups that fimbriectomy could reduce high grade serous ovarian cancer incidence. *Gynecol Oncol* 128:151-152, 2013
22. Westgren M: Prevention of ovarian cancer: Let's do something. *Acta Obstet Gynecol Scand* 9:1009-1010, 2012
23. Leblanc E, Narducci F, Farre I, et al: Radical fimbriectomy: A reasonable temporary risk-reducing surgery for selected women with a germ line mutation of *BRCA1* or *2* genes? Rationale and preliminary development. *Gynecol Oncol* 121:472-476, 2011
24. Rebbeck TR, Lynch HT, Neuhausen SL, et al: Prophylactic oophorectomy in carriers of *BRCA1* or *BRCA2* mutations. *N Engl J Med* 346:1616-1622, 2002
25. Colgan TJ, Murphy J, Cole DE, et al: Occult carcinoma in prophylactic oophorectomy specimens: Prevalence and association with *BRCA* germline mutation status. *Am J Surg Pathol* 25:1283-1289, 2001
26. Carcangiu ML, Peissel B, Pasini B, et al: Incidental carcinomas in prophylactic specimens in *BRCA1* and *BRCA2* germ-line mutation carriers, with emphasis on fallopian tube lesions: Report of 6 cases and review of the literature. *Am J Surg Pathol* 30:1222-1230, 2006
27. Powell CB, Kenley E, Chen LM, et al: Risk-reducing salpingo-oophorectomy in *BRCA* mutation carriers: Role of serial sectioning in the detection of occult malignancy. *J Clin Oncol* 23:127-132, 2005
28. Finch A, Shaw P, Rosen B, et al: Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 *BRCA1* and *BRCA2* carriers. *Gynecol Oncol* 100:58-64, 2006
29. Leeper K, Garcia R, Swisher E, et al: Pathologic findings in prophylactic oophorectomy specimens in high-risk women. *Gynecol Oncol* 87:52-56, 2002
30. Leunen K, Legius E, Moerman P, et al: Prophylactic salpingo-oophorectomy in 51 women with familial breast-ovarian cancer: Importance of fallopian tube dysplasia. *Int J Gynecol Cancer* 16:183-188, 2006



31. Hirst JE, Gard GB, McIlroy K, et al: High rates of occult fallopian tube cancer diagnosed at prophylactic bilateral salpingo-oophorectomy. *Int J Gynecol Cancer* 19:826-829, 2009
32. Laki F, Kirova YM, This P, et al: Prophylactic salpingo-oophorectomy in a series of 89 women carrying a BRCA1 or a BRCA2 mutation. *Cancer* 109:1784-1790, 2007
33. Evans DG, Clayton R, Donnai P, et al: Risk-reducing surgery for ovarian cancer: Outcomes in 300 surgeries suggest a low peritoneal primary risk. *Eur J Hum Genet* 17:1381-1385, 2009
34. Lamb JD, Garcia RL, Goff BA, et al: Predictors of occult neoplasia in women undergoing risk-reducing salpingo-oophorectomy. *Am J Obstet Gynecol* 194:1702-1709, 2006
35. Lu KH, Garber JE, Cramer DW, et al: Occult ovarian tumors in women with BRCA1 or BRCA2 mutations undergoing prophylactic oophorectomy. *J Clin Oncol* 18:2728-2732, 2000
36. Callahan MJ, Crum CP, Medeiros F, et al: Primary fallopian tube malignancies in BRCA-positive women undergoing surgery for ovarian cancer risk reduction. *J Clin Oncol* 25:3985-3990, 2007
37. Olivier RI, van Beurden M, Lubsen MA, et al: Clinical outcome of prophylactic oophorectomy in BRCA1/BRCA2 mutation carriers and events during follow-up. *Br J Cancer* 90:1492-1497, 2004
38. Hermsen BB, van Diest PJ, Berkhof J, et al: Low prevalence of (pre) malignant lesions in the breast and high prevalence in the ovary and fallopian tube in women at hereditary high risk of breast and ovarian cancer. *Int J Gynecol Cancer* 119:1412-1418, 2006
39. Bacha OM, Gregoire J, Grondin K, et al: Effectiveness of risk-reducing salpingo-oophorectomy in preventing ovarian cancer in a high-risk French Canadian population. *Int J Gynecol Cancer* 22:974-978, 2012
40. Reitsma W, de Bock GH, Oosterwijk JC, et al: Support of the "fallopian tube hypothesis" in a prospective series of risk-reducing salpingo-oophorectomy specimens. *Eur J Cancer* 49:132-141, 2013
41. Yates MS, Meyer LA, Deavers MT, et al: Microscopic and early-stage ovarian cancers in BRCA1/2 mutation carriers: Building a model for early BRCA-associated tumorigenesis. *Cancer Prev Res (Phila)* 4:463-470, 2011
42. Salazar H, Godwin AK, Daly MB, et al: Microscopic benign and invasive malignant neoplasms and a cancer-prone phenotype in prophylactic oophorectomies. *J Natl Cancer Inst* 88:1810-1820, 1996
43. Eltabbakh GH, Piver MS, Hempling RE, et al: Laparoscopic management of women with a family history of ovarian cancer. *J Surg Oncol* 72:9-13, 1999
44. Scheuer L, Kauff N, Robson M, et al: Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers. *J Clin Oncol* 20:1260-1268, 2002
45. Finch A, Beiner M, Lubinski J, et al: Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 mutation. *JAMA* 296:185-192, 2006
46. Vicus D, Finch A, Cass I, et al: Prevalence of BRCA1 and BRCA2 germ line mutations among women with carcinoma of the fallopian tube. *Gynecol Oncol* 118:299-302, 2010
47. Domchek SM, Friebel TM, Garber JE, et al: Occult ovarian cancers identified at risk-reducing salpingo-oophorectomy in a prospective cohort of BRCA1/2 mutation carriers. *Breast Cancer Res Treat* 124:195-203, 2010
48. Manchanda R, Abdelraheem A, Johnson M, et al: Outcome of risk-reducing salpingo-oophorectomy in BRCA carriers and women of unknown mutation status. *BJOG* 118:814-824, 2011
49. Powell CB, Chen LM, McLennan J, et al: Risk-reducing salpingo-oophorectomy (RRSO) in BRCA mutation carriers: Experience with a consecutive series of 111 patients using a standardized surgical-pathological protocol. *Int J Gynecol Cancer* 21:846-851, 2011
50. Rabban JT, Mackey A, Powell CB, et al: Correlation of macroscopic and microscopic pathology in risk reducing salpingo-oophorectomy: Implications for intraoperative specimen evaluation. *Gynecol Oncol* 121:466-471, 2011
51. Rhiem K, Foth D, Wappenschmidt B, et al: Risk-reducing salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers. *Arch Gynecol Obstet* 283:623-627, 2011
52. Meeuwissen PA, Seynaeve C, Brekelmans CT, et al: Outcome of surveillance and prophylactic salpingo-oophorectomy in asymptomatic women at high risk for ovarian cancer. *Gynecol Oncol* 97:476-482, 2005
53. Jóhannsson OT, Ranstam J, Borg A, et al: Survival of BRCA1 breast and ovarian cancer patients: A population-based study from southern Sweden. *J Clin Oncol* 16:397-404, 1998
54. Deligdisch L, Gil J, Kerner H, et al: Ovarian dysplasia in prophylactic oophorectomy specimens: Cytogenetic and morphometric correlations. *Cancer* 86:1544-1550, 1999
55. Finch AP, Lubinski J, Møller P, et al: Impact of oophorectomy on cancer incidence and mortality in women with a BRCA1 or BRCA2 mutation. *J Clin Oncol* 32:1531-1533, 2014
56. Greene MH, Piedmonte M, Alberts D, et al: A prospective study of risk-reducing salpingo-oophorectomy and longitudinal CA-125 screening among women at increased genetic risk of ovarian cancer: Design and baseline characteristics—A Gynecologic Oncology Group study. *Cancer Epidemiol Biomarkers Prev* 17:594-604, 2008
57. Skates SJ: Ovarian cancer screening: Development of the risk of ovarian cancer algorithm (ROCA) and ROCA screening trials. *Int J Gynecol Cancer* 22:S24-S26, 2012 (suppl 1)
58. Skates SJ, Mai P, Horick NK, et al: Large prospective study of ovarian cancer screening in high-risk women: CA125 cut-point defined by menopausal status. *Cancer Prev Res (Phila)* 4:1401-1408, 2011
59. Hermsen BB, von Mensdorff-Pouilly S, Berkhof J, et al: Serum CA-125 in relation to adnexal dysplasia and cancer in women at hereditary high risk of ovarian cancer. *J Clin Oncol* 25:1383-1389, 2007
60. Bolton KL, Chenevix-Trench G, Goh C, et al: Association between BRCA1 and BRCA2 mutations and survival in women with invasive epithelial ovarian cancer. *JAMA* 307:382-390, 2012
61. Chen S, Parmigiani G: Meta-analysis of BRCA1 and BRCA2 penetrance. *J Clin Oncol* 25:1329-1333, 2007
62. National Comprehensive Cancer Network: NCCN Clinical Practice Guidelines in Oncology: Genetic/familial high-risk assessment: Breast and ovarian (version 1.2014). [www.nccn.org](http://www.nccn.org)
63. Rabban JT, Krasik E, Chen LM, et al: Multistep level sections to detect occult fallopian tube carcinoma in risk-reducing salpingo-oophorectomies from women with BRCA mutations: Implications for defining an optimal specimen dissection protocol. *Am J Surg Pathol* 33:1878-1885, 2009
64. Medeiros F, Muto MG, Lee Y, et al: The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. *Am J Surg Pathol* 30:230-236, 2006
65. Nicosia SV, Wilbanks GD, Saunders B, et al: Cytology of human ovarian surface epithelial brushings. *Cancer* 102:1-10, 2004
66. Runguang B, Hood BL, Sun M, et al: Novel surgical approaches for sampling the ovarian surface epithelium and proximal fluid proteome. *J Proteome Res* 9:6071-6076, 2010
67. Domchek SM, Gaudet MM, Stopfer JE, et al: Breast cancer risks in individuals testing negative for a known family mutation in BRCA1 or BRCA2. *Breast Cancer Res Treat* 119:409-414, 2010
68. Lavie O, Ben-Arie A, Segev Y, et al: BRCA germline mutations in women with uterine serous carcinoma: Still a debate. *Int J Gynecol Cancer* 20:1531-1534, 2010
69. Brinton LA, Felix AS, McMeekin DS, et al: Etiologic heterogeneity in endometrial cancer: Evidence from a Gynecologic Oncology Group trial. *Gynecol Oncol* 129:277-284, 2013
70. Pennington KP, Walsh T, Lee M, et al: BRCA1, TP53, and CHEK2 germline mutations in uterine serous carcinoma. *Cancer* 119:332-338, 2013
71. Jarboe EA, Miron A, Carlson JW, et al: Coexisting intraepithelial serous carcinomas of the endometrium and fallopian tube: Frequency and potential significance. *Int J Gynecol Pathol* 28:308-315, 2009

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## GLOSSARY TERMS

**BRCA1:** a tumor suppressor gene known to play a role in repairing DNA breaks. Mutations in this gene are associated with increased risks of developing breast or ovarian cancer.

**BRCA2:** a tumor suppressor gene whose protein product is involved in repairing chromosomal damage. Although structurally different from BRCA1, BRCA2 has cellular functions similar to BRCA1. BRCA2 binds to RAD51 to fix DNA breaks caused by irradiation and other environmental agents. Also known as the breast cancer 2 early onset gene.

**CA-125 (cancer antigen 125):** a protein produced by the fallopian tubes, the endometrium, and the lining of the abdominal cavity (peritoneum). CA-125 is a tumor marker present in higher than normal amounts in the blood and urine of patients with certain cancers. Typically, women with ovarian cancer have high levels of CA-125. Other conditions associated with elevated levels of CA-125 include endometriosis, pancreatitis, pregnancy, normal menstruation, and pelvic inflammatory disease. CA-125 levels may be used to help diagnose ovarian cancer and to determine whether these tumors are responding to therapy. The normal range for CA-125 is less than 35 U/mL and less than 20 U/mL for women who have been treated for ovarian cancer. Women with ovarian cancer may show values higher than 65 U/mL.

**logistic regression:** a multivariable regression model in which the log of the odds of a time-fixed outcome event (eg, 30-day mortality) or other binary outcome is related to a linear equation.

**mutation:** a change of one base in a nucleotide sequence that may result in a change in the amino acid sequence.

**Appendix**

The following Gynecologic Oncology Group member institutions participated in the primary research study: Roswell Park Cancer Institute, University of Alabama at Birmingham, Duke University Medical Center, Walter Reed Army Medical Center, Wayne State University, University of Minnesota Medical School, Mount Sinai School of Medicine, University of Mississippi Medical Center, Colorado Gynecologic Oncology Group, University of California at Los Angeles, University of Cincinnati, University of North Carolina School of Medicine, University of Iowa Hospitals and Clinics, University of Texas Southwestern Medical Center at Dallas, Indiana University School of Medicine, Wake Forest University School of Medicine, University of California Medical Center at Irvine, Rush-Presbyterian-St Luke’s Medical Center, Magee Women’s Hospital, University of New Mexico, The Cleveland Clinic Foundation, Washington University School of Medicine, Memorial Sloan Kettering Cancer Center, Cooper Hospital/University Medical Center, Columbus Cancer Council, MD Anderson Cancer Center, University of Massachusetts Medical School, Fox Chase Cancer Center, Women’s Cancer Center, University of Oklahoma, University of Virginia Health Sciences Center, University of Chicago, Mayo Clinic, Case Western Reserve University, Tampa Bay Cancer Consortium, Australia New Zealand Gynaecological Oncology Group Clinical Trials Centre, Yale University, University of Wisconsin Hospital, Women and Infants Hospital, The Hospital of Central Connecticut, and Community Clinical Oncology Program, and Warren G. Magnuson Clinical Center, National Institutes of Health.

**Table A1.** Endometrial Carcinoma Characteristics at Baseline Elective Hysterectomy Performed Concurrently With RRSO

Age (years)	BRCA1/2 Status	Menopausal Status	Family History (No. of patient cases)		Tamoxifen Exposure	Preoperative		Histologic Type	Cytology	Stage
			Ovarian Cancer	Breast Cancer		CA-125	TVU			
51	BRCA1	Post	2	≥ 3	Never	11	Negative	Serous carcinoma	Positive	IIIA
67	BRCA1	Post	0	1	Prior	16	Negative	Serous carcinoma	Negative	IA
44	Negative	Pre	1	2	Never	14	Negative	Mucinous carcinoma	Negative	IA
56	Negative	Post	1	1	Unknown	36	Negative	Mucinous carcinoma	Negative	IB
48	Negative	Pre	1	2	Never	18	Negative	Endometrioid carcinoma	Negative	I
51	Negative	Post	1	0	Never	14	Negative	Endometrioid carcinoma	Negative	IA

Abbreviations: CA-125, cancer antigen 125; RRSO, risk-reducing salpingo-oophorectomy; TVU, transvaginal ultrasound.