Radiologic-Histopathologic Correlation of Transvaginal US and Risk-reducing Salpingo-oophorectomy for Women at High Risk for Tubo-ovarian Carcinoma

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Conflicts of interest are listed at the end of this article.

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Purpose: To examine radiologic-histopathologic correlation and the diagnostic performance of transvaginal US prior to risk-reducing salpingo-oophorectomy (RRSO) in women at high risk for tubo-ovarian carcinoma (TOC).

Materials and Methods: This retrospective study included 147 women (mean age, 49 years; age range, 28–75 years) at high risk for TOC who underwent transvaginal US within 6 months of planned RRSO between May 1, 2007, and March 14, 2018. Histopathologic results were reviewed. Fellowship-trained abdominal radiologists reinterpreted transvaginal US findings by using standardized descriptors. Descriptive statistical analysis and multiple logistic regression were performed.

Results: Of the 147 women, 136 had mutations in BRCA1, BRCA2, Lynch syndrome, BRIP1, and RAD51D genes, and 11 had a family history of TOC. Histopathologic reports showed 130 (88.4%) benign nonneoplastic results, 10 (6.8%) benign neoplasms, five (3.4%) malignant neoplasms, and two (1.4%) isolated p53 signature lesions. Transvaginal US results showed benign findings in 95 (64.6%) women and abnormal findings in 11 (7.5%) women; one or both ovaries were not visualized in 41 (27.9%) women. Hydrosalpinx was absent in all TOC and p53 signature lesions at transvaginal US. Transvaginal US had 20% sensitivity (one of five), 93% specificity (132 of 142), 9% positive predictive value (one of 11), and 97% negative predictive value (132 of 136) for TOC. Cancer was detected in one of five women at transvaginal US, and three of five false-negative lesions were microscopic or very small.

Conclusion: Preoperative transvaginal US had low sensitivity for detecting TOC in women at high risk for TOC. Clinically relevant precursors and early cancers were too small to be detected.

Supplemental material is available for this article.

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Tubo-ovarian cancer (TOC) is the most fatal gynecologic cancer and the fifth most common cause of cancer-related death in women in the United States (1). Survival correlates with the cancer stage at diagnosis. If the disease is localized or regional, the 5-year relative survival rate is 75%–92%; however, if disease is distant, the 5-year relative survival is only 29% (2). Approximately 59% of patients have distant disease at diagnosis (2). Therefore, early detection and prevention are essential to affect survival.

Most TOCs are high-grade serous carcinomas (HGSCs) that commonly arise in the fallopian tube (3) and may originate as precursors known as p53 signature lesions. Further mutations may result in serous tubal intraepithelial carcinoma (STIC), which can spread to the ovary and/or peritoneum directly to develop into HGSC.

The risk of ovarian cancer in the general population is about 1.3% (2). However, certain genetic mutations predispose women to much higher lifetime risk. For example, the cumulative lifetime risks of TOC for BRCA1 and BRCA2 mutation carriers are 36%–59% and 10%–28%, respectively (4–6). These high-risk individuals are offered definitive prevention of TOC by means of risk-reducing salpingo-oophorectomy (RRSO) performed after childbearing or before a consensus-recommended age (range, 35–50 years, depending on the mutation) (7,8).

However, some women may defer undergoing RRSO until beyond the recommended age or decline surgery altogether (9). For these patients, surveillance with combined transvaginal US and the serum marker CA-125 can be considered at the clinician’s discretion, starting at age 30–35 years, according to the National Comprehensive Cancer Network, American College of Obstetricians and Gynecologists, American Cancer Society, and American Society of Clinical Oncology (7,10–15). Although surveillance remains an option, it has no proven benefit because there is no clinically significant effect on survival rate, a high number of false-positive findings may result in harm to the patient owing to unnecessary surgery, and there is increased use of health care resources (7,10,13,16). In addition, small early-stage ovarian cancers are difficult to detect. High-grade serous subtypes can be almost completely
transvaginal US performed prior to risk-reducing salpingo-oophorectomy in women at high risk for tubo-ovarian carcinoma demonstrated poor performance for detecting early-stage cancer.

Key Points
- In women at high risk for tubo-ovarian carcinoma who underwent transvaginal US prior to planned risk-reducing salpingo-oophorectomy, transvaginal US had low sensitivity (20% [one of five]) for predicting malignancy.
- Most cancers were too small to visualize, and most abnormal transvaginal US results were benign at histopathologic analysis. Expansion of other approaches is needed to detect early-stage cancer at routine screening.

Materials and Methods

Study Design
This retrospective study was Health Insurance Portability and Accountability Act compliant and approved by the institutional review board. The requirement to obtain informed consent was waived. The Electronic Medical Record Search Engine (EMERSE) (17) was used to search electronic medical records and obtain a list of all female patients in our electronic medical record with the following inclusion criteria: (a) age 18 years or older; (b) high risk for TOC; (c) transvaginal US performed within 6 months before planned RRSO between May 1, 2007, and March 14, 2018; and (d) transvaginal US, surgery, and histopathologic analysis were performed at our institution. Search terms for finding patients in the EMERSE system are found in Appendix E1 (supplement). The patients' electronic medical records and imaging findings were reviewed manually by M.D.S. to ensure inclusion criteria were met. Of 333 patients found in the search, 180 patients were excluded because they had not yet undergone RRSO or underwent RRSO more than 6 months after transvaginal US. Six additional patients were excluded, each for one of the following reasons: only transabdominal US was performed, the adnexa were not evaluated at US, US images were not available, RRSO was performed before US, only cystectomy was performed, and gastrointestinal carcinoma metastases to the ovaries were present. A total of 147 women were ultimately included in this study. There was no known overlap of these patients with those in prior studies.

Transvaginal US Examinations
All transvaginal US examinations were performed by a registered diagnostic medical sonographer by using one of the following machines: GE LOGIQ 9, GE LOGIQ 700, or GE LOGIQ 900 (GE Healthcare; Waukesha, Wis); Philips iU22 or Philips CX50 (Philips Healthcare; Andover, Mass); Zonare (ZONARE Medical Systems; Mountain View, Calif); Acuson Sequoia, Acuson Antares, or Acuson S2000 (Siemens Healthineers; Mountain View, Calif); or SuperSonic Imagine Aixplorer (SuperSonic Imagine; Aix-en-Provence, France). Examinations included transabdominal (3–6-MHz) and transvaginal (6–8-MHz) pelvic US, with gray-scale static and cine imaging performed in all examinations, and color, power, and/or spectral Doppler US were performed as deemed appropriate at the time of examination by the sonographer and interpreting radiologist. The imaging protocol used was constant during the study period. Images were stored and reviewed on a Syngo Dynamics (Siemens Healthineers) picture archiving and communication system.

Transvaginal US Image Assessment
Five abdominal radiologists with fellowship training in abdominal radiology (N.E.C., W.R.M., M.M.L., E.B.S., and A.P.W., with 1, 2, 8, 2, and 8 years of postfellowship experience, respectively) reinterpreted the transvaginal US studies in July and August of 2018. Research interpretation was performed in pairs to reach consensus impressions such that each reader was paired with another reader twice and reviewed approximately 30% of the cases. A consensus could be reached with a third reader from the group if needed. For research interpretations, adnexa were assessed by using terms from the 2018 published lexicon of the Ovarian-Adnexal Reporting and Data System (O-RADS) for US and the 2008 International Ovarian Tumor Analysis (IOTA) simple rules, which include evidence-based descriptors to differentiate benign and malignant adnexal masses (18,19). Readers assigned a final level of suspicion (benign, indeterminate, or possibly malignant) per adnexum by using the O-RADS for US lexicon and IOTA simple rules; then, an overall categorization was assigned for each patient on the basis of the adnexum with the highest level of suspicion. Indeterminate and possibly malignant findings were considered abnormal in the final analysis. Cysts
and physiologic findings were categorized as benign. Uterine, cervical, tubal, and peritoneal findings also were catalogued. The readers were aware that the patients were at high risk for TOC, just as an interpreting radiologist would be in a screening setting. However, the readers were blinded to the original interpretations and histopathologic findings.

**Immunohistochemistry and Histologic Assessment**

Most surgical procedures were performed laparoscopically by using a standardized surgical approach and included peritoneal washings in all cases (20). Histopathologic results were obtained by means of chart review. For assessment of all specimens, the fallopian tubes and ovaries from each patient were grossly inspected and processed in their entirety for microscopic analysis. This was accomplished by thinly sectioning (2–3-mm-thick slices) through the fallopian tubes and ovaries of the patients at high risk. All specimens were analyzed by pathologists with subspecialty experience in gynecologic pathology. For diagnostic classification of p53 signature lesions, STIC, and serous tubal intraepithelial lesions, a widely accepted algorithm used to classify tubal precursor lesions was applied (21). This algorithm uses morphologic and immunophenotypic parameters, with the latter based on p53 and Ki-67 immunostaining. STIC is composed of segments of at least 12 cells (with or without intervening ciliated cells) of cytologically atypical tubal epithelial cells with aberrant p53 immunostaining (according to criteria, >75% show strong and/or diffuse or completely absent p53 immunoreexpression) indicative of a mutant phenotype and a Ki-67 proliferation index of greater than 10%. Serous tubal intraepithelial lesions comprise cytologically atypical tubal epithelial cells with aberrant p53 immunostaining but without increased proliferative activity; less than 10% of cells are positive for Ki-67 at immunohistochemical analysis. p53 Signature lesions represent segments of otherwise normal-appearing fallopian tube epithelial cells that show aberrant p53 immunostaining without increased proliferative activity.

Immunohistochemical analysis for p53 (clone: DO-7; Ventana Medical Systems, Tucson, Ariz) and Ki-67 (clone: MIB1; Ventana Medical Systems) immunostaining was performed at the discretion of the pathologist by using 4-μm–thick formalin-fixed, paraffin-embedded tissue sections. Of note, the number of p53 signature lesions in this population may be underestimated because the designation of these lesions as potentially clinically significant precursors became recognized during the study period and the exact time that the reporting of these lesions began in our department is unknown.

**Other Clinical Characteristics**

Medical records were reviewed to obtain the following data: demographics; operative report findings regarding the ovaries and fallopian tubes, and the uterus and/or cervix if it was removed; risk factors for TOC; and serum CA-125 levels, if obtained within 12 months of RRSO. In addition, history of endometriosis prior to or diagnosed at surgery, history of breast cancer, relevant surgical history, when available; and gravidity and parity histories were acquired.

**Statistical Analysis**

Descriptive statistical analyses were performed. Radiologic-histopathologic correlation was assessed on a per-adnexum basis, and the diagnostic performance of transvaginal US was analyzed on a per-patient basis as if in a clinical setting. Multiple logistic regression was also performed to evaluate the effect of predictors (including age, race, personal history of breast cancer, and presence of a sonographic abnormality) on the pathologic outcome of TOC. The CA-125 value was not included owing to a substantial amount of missing data. Obligate inclusion rather than a variable selection method was used to create the model because all predictors were considered biologically relevant. \( P < .05 \) indicated standard statistical significance throughout. Statistical analyses were performed by using Excel (Microsoft; Redmond, Wash) and SAS, version 9.4 (SAS Institute; Cary, NC) software.

**Results**

**Demographics and Surgical Timing**

The patient population consisted of 147 women with a mean age of 49 years (age range, 28–75 years). The mean number of prior pregnancies was 2.6 (range, 0–11 pregnancies), and the mean number of births was 1.2 (range, 0 to five births). Racial distribution included 88.4% White, 5.5% Asian, 4.1% African American, and 2% unknown. Reasons for planned RRSO were known oncogenic and/or likely variants in known ovarian cancer genes in 136 of 147 (92.5%) of the women and a strong family history of TOC in 11 of 147 (7.5%) of them. Distribution of genetic risk factors per patient included mutations in \( BRCA1 \) (64 of 147 [43.5%]), \( BRCA2 \) (57 of 147 [38.8%]), \( BRIP1 \) (three of 147 [2%]), and \( RAD51D \) (one of 147 [0.7%]) genes and Lynch syndrome (11 of 147 [7.5%]). Mutations related to Lynch syndrome included mutations in \( MLH1 \) in one patient, in \( MSH2 \) in two patients, in \( MLH1 \) and \( MSH2 \) in one patient, and in \( MSH6 \) in one patient, with the mutation not specified in six patients. Endometriosis was present in 18 of 147 (12.2%) patients according to prior history or at the time of RRSO, and 74 of 147 (50.3%) patients had a personal history of breast cancer. Relevant surgical history included five of 147 (3.4%) patients who underwent unilateral salpingectomy, two of 147 (1.3%) who underwent unilateral salpingo-oophorectomy and unilateral salpingectomy, and two of 147 (1.3%) who underwent unilateral salpingo-oophorectomy.

All 147 patients had undergone at least salpingo-oophorectomy. Of the 147 patients, 98.6% (145 of 147) underwent planned RRSO, 1.4% (two of 147) underwent staging surgery for suspected TOC owing to transvaginal US and frozen-section specimen results, and 2% (three of 147) underwent staging surgery for endometrial carcinoma owing to transvaginal US and/or endometrial biopsy results. The mean elapsed time between transvaginal US and RRSO was 48 days (range, 1–176 days). The average delay in undergoing RRSO until an age beyond that recommended in National Comprehensive Cancer Network guidelines was 6.1 years for all patients, 6.3 years for patients without TOC (range, 12 [early] to 35 [delayed] years), and 2.4...
years for patients with TOC (range, 8 [early] to 12 [delayed] years). There was no statistically significant difference between the delay in undergoing RRSO between the patients with and those without TOC ($P = .372$).

**Adnexal Preoperative Transvaginal US Results**

On a per-patient basis, transvaginal US findings of the adnexa were interpreted as benign in 64.6% (95 of 147) of the women and as abnormal in 7.5% (11 of 147) of them. One or both ovaries were not adequately visualized in 27.9% (41 of 147) of the women. It is unknown why ovary visualization was limited in this number of patients, but it may be because a similar number of women, approximately 35%, were estimated to have been postmenopausal and thus have ovaries that were smaller and more difficult to visualize. This estimate is based on the number of women included in the study who were older than 51 years, which is the average age of menopause (22). In addition, in 2.7% (four of 147) of the patients, an ovary had already been surgically removed.

**Adnexal Histopathologic Results**

At final histopathologic analysis, 88.4% (130 of 147) of the women had benign nonneoplastic findings in the ovaries and fallopian tubes. Benign neoplasms were present in 6.8% (10 of 147) of patients: eight women with cystadenomas or cystadenofibromas, one with a Sertoli-Leydig cell tumor, and one with a mature teratoma. Malignant neoplasms were present in 3.4% (five of 147) of women, including one with STIC (stage 0), who also had a contralateral p53 signature lesion, and four with HGSCs (stages IA, IA, IC, and IIIIC). Isolated p53 signature lesions were present in 1.4% (two of 147) of the women.

**Adnexal Preoperative Transvaginal US and Histopathologic Results**

The distribution of transvaginal US and histopathologic results is presented in Table 1. For patients in whom both ovaries were visualized, radiologic-histopathologic correlation showed that transvaginal US enabled the correct identification of 91 of 101 true-negative (benign nonneoplastic findings, benign neoplasms, and p53 signature lesions) results but only one of five true-positive (malignant neoplasms) results. In clinical practice, nonvisualization of the ovaries and p53 signature lesions is considered to represent negative results, as no further action is typically taken. Therefore, when only abnormal transvaginal US findings are considered positive results and nonvisualization of the ovaries and p53 signature lesions represents negative results, the sensitivity of transvaginal US for detecting TOC per patient is 20% (one of five), with a specificity of 93% (132 of 142), positive predictive value (PPV) of 9% (one of 11), and negative predictive value (NPV) of 97% (132 of 136). In the 147 women, one result was true positive, 10 results were false positive, four were false negative, and 132 were true negative.

While the accuracy and resolution of transvaginal US were not expected to change during the study, for evaluation of potential differences in sensitivity arising from technical advances in US, the time span was divided evenly into a remote group (January 2005 to August 2011) and a recent group (September 2011 to March 2018). For the 34 remote transvaginal US examinations, sensitivity was 0% (0 of two), specificity was 90.6% (29 of 32), the PPV was 0% (0 of three), and the NPV was 93.5% (29 of 31). Of the 34 results of these examinations, none was true positive, three were false positive, two were false negative, and 29 were true negative. The 113 recent transvaginal US examinations had a sensitivity of 33.3% (one of three), a specificity of 93.6% (103 of 110), a PPV of 12.5% (one of eight), and a NPV of 98.1% (103 of 105). Of the 113 recent examination results, one was true positive, seven were false positive, two were false negative, and 103 were true negative. Diagnostic performance was overall similar between the two groups, but the small number of malignancies prevents a meaningful statistical comparison.

Transvaginal US findings in cases with malignant and/or p53 signature lesions are shown in Table 2. Most cases had discordant radiologic-histopathologic correlation for predicting malignancy or p53 signature lesions. This may be because these lesions were microscopic and/or tubal in location and hence difficult to visualize. In nine involved adnexa, six lesions were isolated to the fallopian tubes, five were microscopic, and one was smaller than 0.1 cm. The only concordant malignant case was that of bilateral 9- and 8-cm hypervascular solid adnexal masses with ascites at transvaginal US, corresponding to bilateral HGSC (stage IIIC) involving the ovaries (Fig 1). This patient underwent staging surgery as a result of the transvaginal US findings. The only other case with findings that potentially could have been positive at transvaginal US was that of a 6-cm unilocular cyst that was simple appearing but had a sonographically occult 0.6-cm malignant (stage IA) mural nodule (Fig 2).

**Table 1: US and Histopathologic Results**

| Adnexal Histopathologic Results | Normal or Physiologic Findings | Abnormal Sonographic Findings | Nonvisualization of One or Both Ovaries |
|--------------------------------|-------------------------------|-------------------------------|----------------------------------------|
| Benign nonneoplastic (n = 130) | 85                            | 9                             | 36                                     |
| Benign neoplasm (n = 10)      | 5                             | 1                             | 4                                      |
| p53 Signature lesion (n = 2)  | 1                             | 0                             | 1                                      |
| Malignant neoplasm (n = 5)    | 4                             | 1                             | 0                                      |

Note.—Data are numbers of single results per patient.
This patient initially underwent RRSO and then required subsequent staging surgery. Hydrosalpinx was not seen at transvaginal US in any patients with malignant or p53 signature lesions, including those cases when these lesions were present only in the fallopian tubes at histopathologic analysis.

Descriptions from 10 false-positive transvaginal US assessments, and the respective histopathologic findings, are presented in Table 3. One patient had a 6.6-cm solid mass with marked vascular flow that proved to be a benign Sertoli-Leydig cell tumor. This was the only patient with a benign neoplasm and positive transvaginal US result. This patient also underwent staging surgery as a result of the transvaginal US findings and a false-positive frozen-section specimen. Five patients underwent RRSO less than two menstrual cycles (maximum, 36 days) after transvaginal US, and all findings correlated with hemorrhagic cysts, benign cysts, or benign hydrosalpinges. Four patients had more than two menstrual cycles between transvaginal US and RRSO or were postmenopausal, and their findings either resolved or were similarly benign.

### Multiple Logistic Regression Analysis for TOC

At multiple logistic regression analysis, a model including biologically relevant covariates, including age, race, personal history of breast cancer, and presence of a sonographic abnormality, was poorly predictive of the outcome of TOC ($P = .99$ for global null hypothesis; C statistic, 0.66). None of the individual covariates (non-White race [$P = .99$], age [$P = .67$], breast cancer history [$P = .36$], US result [$P = .34$]) was a statistically significant independent predictor of malignancy.

### Preoperative CA-125 Level and Uterine Preoperative and Histopathologic Results

Owing to substantial missing data, results of preoperative serum CA-125 level measurements, preoperative uterine trans-
Transvaginal US and Risk-reducing Salpingo-oophorectomy for Women at High Risk for Tubo-ovarian Carcinoma

In this retrospective study involving 147 women at high risk for TOC who underwent RRSO, we found that preoperative transvaginal US had poor diagnostic performance for detecting TOC, with only 20% (one of five) sensitivity. Results were comparable to those in other studies. For example, a sensitivity of 16% was found in a larger-scale study of 900 patients (23), who also were at high risk for TOC and had undergone transvaginal US prior to RRSO. The prevalence of malignant disease in our study was low (3.4%), but this was expected because a prevalence of 2.3%–5.7% has been reported in most other studies in which histopathologic results from RRSO were assessed (23–27). The low prevalence accounts for the high NPV (97% [132 of 136]). Unlike other studies in which histopathologic and transvaginal US results in patients at high risk for TOC are evaluated, this study involved direct radiologic-histopathologic correlation on a per-adnexum basis.

These study results show that transvaginal US alone has low sensitivity as a preoperative tool for detecting small cancers. However, transvaginal US could be performed with the intent of identifying overt preexisting TOC. Identifying potential malignancy can help determine whether the surgery will be a routine, (usually) laparoscopic RRSO or plans for frozen section acquisition or staging surgery performed by a surgeon with gynecologic-oncologic expertise should be made. Reducing the need for subsequent staging surgeries potentially could result in reductions in the morbidity and mortality associated with additional surgery, time to treatment, and cost. Further analyses of morbidity, mortality, and cost-effectiveness are needed.

However, in routine screening settings, the detection of these small tumors and the features of tumors are crucial. On the basis of findings of other RRSO specimens, it is estimated that a 50% reduction in mortality may require the detection of 0.5-cm neoplasms owing to microscopic or small size and/or a tubal location of most tumors. The only concordant malignant case involved large hypervascular solid adnexal masses (Fig 1). A discordant malignant case was that of a large simple unilocular cyst with a small sonographically occult mural nodule (Fig 2). US is known to have limitations for evaluating the entire inner wall of larger lesions (28,29), although the risk of malignancy in a unilocular ovarian cyst is extremely low in an average-risk population (30,31).

Our findings suggest that the scope of preoperative transvaginal US performed prior to planned RRSO is limited for detecting small cancers. However, transvaginal US could be performed with the intent of identifying overt preexisting TOC. Identifying potential malignancy can help determine whether the surgery will be a routine, (usually) laparoscopic RRSO or plans for frozen section acquisition or staging surgery performed by a surgeon with gynecologic-oncologic expertise should be made. Reducing the need for subsequent staging surgeries potentially could result in reductions in the morbidity and mortality associated with additional surgery, time to treatment, and cost. Further analyses of morbidity, mortality, and cost-effectiveness are needed.

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Figure 1: Concordant radiologic-histopathologic correlation of high-grade serous carcinoma (HGSC) (stage IIIC) in a 36-year-old woman who had BRCA1 mutation with bilateral 9- and 8-cm vascular solid adnexal masses and ascites at preoperative transvaginal US. (a) Sagittal (SAG) transvaginal US image of the right (RT) adnexa (ADN) shows a hypoechoic circumscribed solid mass. (b) Coronal (COR) transvaginal color Doppler US image of the left (LT) adnexa (ADN) shows a contralateral solid mass with marked vascularity. (c) Photomicrograph of benign left fallopian tube (black arrow) compressed by an expansile ovarian mass comprising HGSC (white arrow). (Hematoxylin-eosin stain; original magnification, ×20.) (d) Photomicrograph of benign left fallopian tube (black arrow) adjacent to HGSC of the ovary (white arrow). (Hematoxylin-eosin stain; original magnification, ×40.)
tumors, while the median size of tumors associated with stage III or IV disease is only 3 cm (32). However, in our study, most of the histopathologically detected lesions were too small to visualize sonographically and the sensitivity of transvaginal US for detecting malignant lesions was only 20%, while a sensitivity threshold of 75% has been suggested to constitute appropriate screening for TOC in a high-risk population (33).

Multiple prospective large-scale studies of screening transvaginal US in patients with average risk have not demonstrated a mortality benefit (16,34,35). Screening may even pose harm, with a substantial number of major surgical complications resulting from false-positive cases (16). Despite these risks, several organizations support offering screening transvaginal US to high-risk women (7,10–15). In some screening studies involving high-risk patients with a genetic or family history, a stage shift has been observed, with the diagnosis at earlier stages. However, these benefits are undermined by coexistent observations that more than half of detected cancers are advanced, imaging-occult malignancies are found in RRSO specimens, and interval cancers occur (36–38).

Our study had a number of limitations. Although evaluation of serum marker CA-125 levels is currently used in conjunction with transvaginal US for screening, we were unable to incorporate this measurement because only 43% (63 of 147) of patients had undergone serum CA-125 level measurement within 12 months of RRSO. Because serial examinations were not performed, this analysis differed from that in a true screening setting. The sensitivity was lower than that in studies involving serial examinations and CA-125 measurements in patients of all risk levels and at high risk (39,40). While the prevalence of malignancy was consistent with that in prior studies, there were only five malignant cases for analysis. Risk factor modification, such as oral contraceptive use, could not be accounted for. In approximately 28% of women, one or both ovaries could not be visualized, although this could have been a function of limited identification owing to small size in the postmenopausal population (approximately 35% of patients). In addition, the degree of nonvisualization further emphasizes the limitations of transvaginal US as a screening modality, as the age of the screening population could extend well into the postmenopausal years.

Our findings underscore the need for improved methods for early detection of TOC. Neuer and emerging advanced technology includes photoacoustic US, contrast-enhanced sonography, molecular imaging, and radiomics (33,41–43). Investigation of so-called liquid biopsy to detect circulating tumor cell particles,

**Figure 2:** Discordant radiologic-histopathologic correlation of high-grade serous carcinoma (HGSC) (stage IA) in a 53-year-old woman with BRIP1 mutation. (a) Sagittal (SAG) transvaginal US image of the right (RT) adnexa demonstrates a large unilocular simple cyst. OV = ovary. (b) Transverse color Doppler US image of the right adnexa does not demonstrate vascularized soft-tissue components; however, histopathologic analysis revealed a 0.6-cm malignant mural nodule. (c) Photomicrograph of the same simple ovarian cyst (white arrow denotes outer serosal surface of cyst) colonized on the inner surface by HGSC (black arrow). (Hematoxylin-eosin stain; original magnification, ×40.) (d) Photomicrograph of the inner surface of the same ovarian cyst (black arrow denotes benign serosal mesothelial cells) colonized by HGSC (white arrow). (Hematoxylin-eosin stain; original magnification, ×200.)
including RNA and/or DNA particles, proteins, and autoantibodies, in addition to multimarker analysis and proteomics, continues (33,43).

In conclusion, preoperative transvaginal US exhibited low sensitivity for detection of TOC in women at high risk for TOC who underwent RRSO. Tiny tubal precursors and early-stage carcinomas are poorly assessed at transvaginal US, and new screening modalities are needed to improve the early detection of TOC. There is little evidence to support the use of transvaginal US for routine adnexal screening in women at high risk for TOC.

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