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¹Peritoneal washing cytology in patients with BRCA1 or BRCA2 mutations undergoing risk-reducing salpingo-oophorectomies: A 10-year experience and reappraisal of its clinical utility

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Abstract

Objective—To evaluate the utility of peritoneal washing cytology (PWC) for detecting occult primary peritoneal carcinoma in patients with BRCA1 or BRCA2 mutations, we reviewed PWCs obtained during risk-reducing salpingo-oophorectomy (RRSO) from 117 patients at our institution and correlated the results with surgical pathology findings.

Methods—Records of 128 PWCs from 125 patients with BRCA1 or BRCA2 mutations undergoing RRSO at MD Anderson Cancer Center between 2000 and 2010 were obtained. Slides were available for review for 119 PWCs from 117 patients (2 patients had 2 PWCs each). Cytopathologists, blinded to the RRSO histopathologic diagnoses, categorized the PWCs as benign, atypical, suspicious for malignancy, or malignant. These results were correlated with the RRSO histopathologic diagnoses.

Results—PWCs from 113 patients were benign. Of the remaining 4 patients, 2 had PWCs classified as atypical, 1 as suspicious for malignancy, and 1 as malignant. The corresponding RRSO histopathologic findings of the 2 atypical PWCs showed endosalpingiosis and cystadenofibroma in one case and showed no abnormalities in the other case. Both patients with suspicious or malignant PWCs, indicating the possibility of occult peritoneal carcinoma, had RRSO histopathologic diagnoses of endometriosis and endosalpingiosis. Nine patients had abnormal tubal or ovarian histologic findings, but all 9 of these patients had benign PWCs.

Conclusion—PWC has the potential to detect occult peritoneal carcinoma in patients with BRCA1 or BRCA2 mutations. The clinical significance of a positive PWC without abnormal RRSO histology remains unclear and will require long-term follow-up for determination.

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Conflict of Interest Statement

The authors declare that there are no conflicts of interest.

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Keywords

peritoneal washing; cytology; BRCA; salpingo-oophorectomy; occult ovarian carcinoma

Introduction

Patients with BRCA1 and BRCA2 mutations have a 36–63% and 10–27% lifetime risk, respectively, of developing a BRCA-associated gynecologic (ovarian, fallopian tube, or primary peritoneal) cancer [1–4] and a 56–84% lifetime risk of developing breast cancer [1, 5, 6]. Because of these risks, the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology recommend that women with BRCA1 or BRCA2 mutations undergo risk-reducing salpingo-oophorectomy (RRSO), ideally between 35 and 40 years of age, or when childbearing is completed [7]. Some studies have shown that RRSO decreases the risk of developing coelomic cancers in women with BRCA1 or BRCA2 mutations by as much as 96% [8]. However, following RRSO, these patients still have a 1–6% estimated lifetime risk of a primary peritoneal carcinoma (PPC) [9, 10].

Performing abdomino-pelvic washings with saline for peritoneal washing cytology (PWC) at the time of RRSO has been recommended to screen for the presence of occult PPC and peritoneal spread from occult carcinomas of the ovaries or fallopian tubes [11–15]. While many reports have described the RRSO histopathology in numerous patients [8, 9, 15–28], the results of the concurrently acquired PWCs have been detailed in relatively few studies and in limited numbers of patients [9, 14, 15, 17, 18, 22, 29, 30]; therefore, the prognostic significance of PWC results characterized as malignant remains uncertain. Moreover, many of the patients in these PWC studies were either negative for or not tested for BRCA mutations and had opted for RRSO because of a strong family history of breast and/or ovarian cancer; thus, the prognostic value of PWC in patients with BRCA1 or BRCA2 mutations remains unknown. To address this gap in knowledge, we evaluated the utility of PWC in the setting of RRSO in a study cohort limited to patients with documented BRCA1 or BRCA2 germline mutations because these are the patients most at risk for harboring an occult PPC, the detection of which is the prime reason for doing PWC. We retrospectively reviewed the PWC slides from 117 patients with BRCA1 or BRCA2 mutations who had undergone RRSO at our institution over a 10-year period, and we correlated the results with surgical pathology findings and patient outcome data.

Materials and methods

From a search of our electronic database, records of 128 PWCs from 125 women with known BRCA1 and/or BRCA2 germline mutations who underwent RRSO at The University of Texas MD Anderson Cancer Center between August 2000 and June 2010 were obtained. Pelvic/peritoneal malignancies were not suspected in any of these patients, and none had an elevated CA-125 level prior to undergoing RRSO.

Peritoneal washings had been obtained in the following manner: As soon as the peritoneal cavity was opened, any free fluid was aspirated, and the peritoneal surfaces were lavaged with warm physiologic saline. The fluid was then aspirated and sent immediately to the cytopathology laboratory. There it was centrifuged and the Shandon Cytospin was used to prepare slides from the resuspended cell pellet after the supernatant was decanted. The slides were fixed in modified Carnoy's solution and stained using the Papanicolaou method.

Slides were available for our review for 119 PWCs from 117 patients (2 patients had 2 PWCs each). Cytopathologists, blinded to the RRSO histopathologic diagnoses, categorized the PWC results as benign, atypical, suspicious for malignancy, or malignant. The presence

of endosalpingiosis and psammomatous microcalcifications was also noted using previously published criteria [31–33].

The PWC results were then compared with the RRSO histopathologic diagnoses that had been recorded by a gynecologic pathologist. In all cases, ovaries and fallopian tubes had been processed in toto for microscopic examination; however, some of these examinations took place before the adoption of the SEE-FIM protocol proposed by Lee et al. [34, 35].

This study was approved by MD Anderson Cancer Center's Institutional Review Board (Protocol Lab06-0596).

Results

Of the 117 patients whose PWC slides were available for review, 66 had BRCA1 mutations and 51 had BRCA2 mutations. No patients had both BRCA1 and BRCA2 mutations.

PWCs from 113 of the 117 patients were characterized as benign. Of the remaining 4 patients, 2 had PWC findings classified as atypical, 1 as suspicious for malignancy, and 1 as malignant.

For the 2 patients whose PWC diagnoses were atypical, the corresponding histopathologic findings from RRSO specimens were endosalpingiosis and a small serous cystadenofibroma in 1 case and no abnormalities in the other case. The patient with endosalpingiosis and serous cystadenofibroma continued on hormonal therapy for previously diagnosed invasive breast carcinoma and had no evidence of disease and a normal CA-125 level at 28 months' follow-up. The patient with no abnormal histopathologic findings had a bilateral mastectomy for a 7-mm triple-negative breast carcinoma 3 years after the RRSO and had no evidence of disease and a normal CA-125 level at 72 months' follow-up (Table 1).

The patient who had a PWC diagnosis that was suspicious for carcinoma had completed chemotherapy for invasive ductal carcinoma 6 weeks before she underwent RRSO. Her RRSO specimen contained extensive uterine serosal and bilateral ovarian endometriosis and bilateral ovarian endosalpingiosis. She was prescribed anastrozole following the RRSO and had no evidence of disease and a normal CA-125 level at 27 months' follow-up (Table 1).

The 1 patient in our series whose PWC was positive for adenocarcinoma had an RRSO with hysterectomy specimen that did not reveal a source for the adenocarcinoma. Rigorous examination of the surgical specimen had been performed, including complete "blocking in" of bilateral fallopian tubes and ovaries with multiple levels of those tissue blocks examined. The pathologic findings were a few small uterine leiomyomas, adenomyosis, bilateral ovarian endosalpingiosis and endometriosis involving 1 oviduct. After 4 senior cytopathologists had reviewed the PWC with the tissue findings, and following deliberation by a multidisciplinary team of physicians, the patient was presumed to harbor an incidentally discovered PPC, for which she subsequently received 4 cycles of paclitaxel and carboplatin. A "second look" laparoscopy was done, and results of all washings and biopsies were negative for malignancy. Nearly 10 years later, the patient had no evidence of disease and a normal CA-125 level (Table 1).

Nine patients had RRSO specimens with relevant abnormal tubal or ovarian histologic findings. Four of these patients had tubal hyperplasia with atypia, 2 had tubal high-grade serous carcinoma (1 with tumor limited to the mucosa and the other with tumor extending into the submucosa), and 3 had ovarian serous tumors of low malignant potential (Table 2). All 9 of these patients, however, had PWC diagnoses classified as benign.

Discussion

In this 10-year retrospective study of PWC in 117 patients with BRCA1 or BRCA2 mutations who had undergone RRSO, 1 patient with malignant cells revealed by PWC but no malignancy found in the hysterectomy with RRSO surgical specimen was presumed to have PPC. A review of the literature reveals 2 similar cases of occult PPC diagnosed by PWC in patients undergoing RRSO. In the study by Finch et al. [9], 1 of 11 patients with BRCA1 or BRCA2 mutations with tubal, ovarian, or peritoneal carcinomas found at the time of RRSO had malignant cells found by PWC with no source found in the RRSO specimen. However, this study did not include any other PWC data. In a study by Colgan et al. [14], 1 of 3 patients with occult carcinomas found at RRSO had malignant cells identified only in the PWC, but this patient's BRCA mutation status was unknown. The findings of all published studies of PWC in patients with BRCA1 or BRCA2 mutations undergoing RRSO, including our present results, are summarized in Table 3.

Of interest, in our study, all 9 patients with relevant tubal or ovarian histologic findings had PWC results classified as benign. The benign PWC results in the 2 cases with high-grade serous carcinoma likely reflect the early stage of disease in these patients or inherent characteristics of the tumor; however, issues affecting the sampling of peritoneal surfaces, such as volume of saline used and sites of peritoneum washed, may have played a part in the false-negative results.

The biologic sequelae in BRCA1 or BRCA2 mutation-positive patients with PWC results classified as malignant and negative RRSO histopathology findings are, as yet, undefined due to the small number of reported cases and limited follow-up. In the case reported by Colgan et al. [14], the patient received chemotherapy and a second laparotomy following RRSO and had no evidence of disease 10 months after undergoing RRSO. In our case, the patient was also treated with chemotherapy and had no evidence of disease at 118 months' follow-up.

Because of the potential implications of PWC results that are characterized as malignant, especially in the absence of tubal/ovarian carcinoma in the RRSO specimen, the PWC should be carefully assessed and pathologists should be aware of potential diagnostic errors and mitigating factors before classifying the PWC as malignant. Diagnostic pitfalls in the interpretation of peritoneal washings have been well described [31, 32, 36–38] and include reactive mesothelial cells as well as cells derived from endosalpingiosis, endometriosis, and treatment-induced cytologic changes. Careful attention to the peritoneal washings' cytologic characteristics and comparison with clinical and histologic findings should help avoid a misdiagnosis.

Additionally, peritoneal washings may become contaminated by endometrial or endosalpingeal cells during laparoscopically assisted procedures in which a uterine manipulator is used [39]. Because patients with BRCA1 or BRCA2 mutations have a propensity to develop foci of dysplasia or in situ carcinoma in their distal oviducts, the possibility of a false-positive PWC resulting from endosalpingeal-derived dysplastic or malignant cells that may become mechanically dislodged during RRSO and contaminate the peritoneal washing samples is of heightened concern [40]. Such mitigating factors may have been present in the 2 patients reported by Paley et al. [30]; although both patients had PWC described as "copiously positive for malignant cells," the histologic findings were limited to minimal tubal adenocarcinomas (1 patient had an 8-mm-long segment of adenocarcinoma in situ; the other had a 7-mm focus of papillary serous adenocarcinoma without extension to the serosa).

In conclusion, in this largest series to date of PWC in patients with BRCA1 or BRCA2 mutations undergoing RRSO, PWC positive for malignancy was found to be extremely rare, occurring in less than 1% of such patients. In light of the various pitfalls that can lead to an erroneous diagnosis and interpretation, it is essential that malignant PWC results be critically reviewed prior to the formulation of therapy recommendations. While PWC has the potential to detect occult peritoneal carcinoma in patients with BRCA1 or BRCA2 mutations undergoing RRSO, longer follow up data and studies of larger numbers of patients are needed in order to determine the clinical significance of PWC results.

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Highlights

- Peritoneal washing cytology (PWC) from BRCA mutation-positive patients who underwent risk-reducing salpingo-oophorectomies were reviewed
- Two patients had suspicious or malignant PWC but had no malignant histopathologic findings in their surgical specimens
- The clinical significance of a positive PWC without abnormal RRSO histology remains unclear

Table 1
Histopathology of RRSO and clinical follow-up of patients with BRCA1 or BRCA2 mutations and abnormal PWC diagnoses

Patient	PWC diagnosis	RRSO diagnoses	Post-RRSO therapy	Clinical follow-up	Follow-up time (m)
No. 1	Atypical	Endosalpingiosis – both ovaries Serous cystadenofibroma – right ovary	Hormonal therapy for prior breast carcinoma	NED, normal CA-125	28
No. 2	Atypical	No abnormal findings	Bilateral mastectomy for 7- mm triple-negative breast carcinoma 3 y after RRSO	NED, normal CA-125	63
No. 3	Suspicious	Endosalpingiosis – both ovaries Endometriosis – uterine serosa, both ovaries	Hormonal therapy for prior breast carcinoma	NED, normal CA-125	27
No. 4	Malignant	Endosalpingiosis – both ovaries Endometriosis – left oviduct	Chemotherapy for presumed PPC	NED, normal CA-125	118

PWC, peritoneal washing cytology; RRSO, risk-reducing salpingo-oophorectomy; NED, no evidence of disease; PPC, primary peritoneal carcinoma

Table 2

Nine patients with abnormal findings on RRSO histopathology but benign PWC

RRSO histologic diagnosis	No. patients	PWC diagnosis
Tubal hyperplasia with atypia	4	Benign
Tubal high-grade serous carcinoma limited to mucosa	1	Benign
Tubal high-grade serous carcinoma extending into submucosa	1	Benign
Ovarian serous tumor of Low Malignant Potential	3	Benign

PWC, peritoneal washing cytology; RRSO, risk-reducing salpingo-oophorectomy

Table 3

Summary of studies of PWC in patients with undergoing RRSO

Study year	Authors	Total no. pts	No. pts with BRCA1 or BRCA2 mutations	Total no. pts with PWC	No. pts with positive PWC	Concurrent histology for pts with positive PWC	Clinical course	Follow-up
2001	Paley et al. [1]	2	2	2	2	1st - in situ adenocarcinoma R tube; 2nd - 7-mm serous carcinoma L tube	Both - 6 cycles chemotherapy; 1st - negative second-look laparotomy, recurrence, salvage chemotherapy	1st - AWD at 30 m; 2nd - NED at 48 m
2002	Colgan et al. [2]	35	28	35	3 (2 pts had BRCA1 mutation, 1 pt had unknown BRCA status)	1st - BRCA1 mutation, multiple foci of high-grade serous carcinoma in fallopian tube, uterine serosa, ovarian serosa and cortex; 2nd - BRCA1 mutation, single focus of in-situ adenocarcinoma in tubal fimbria; 3rd - negative RRSO specimen	1st - chemotherapy, negative second-look laparotomy; 2nd - no further therapy; 3rd - chemotherapy, negative second-look laparotomy	1st - NED at < 1 y; 2nd - NED at 1 y; 3rd - NED at 10 m
2006	Leunen et al. [3]	51	24	28 (not stated which were from pts with BRCA mutations)	0			
2010	Haldar et al. [4]	113	44	110	2 (both had BRCA1 mutation)	Both positive for PPC	Both - chemotherapy for stage III disease	Not known
2012	Present study	117	117	117	1 (BRCA1 mutation)	Bilateral ovarian endosalpingiosis, L ovarian endometriosis	Chemotherapy for presumed PPC	NED at 118 months

PWC, peritoneal washing cytology; RRSO, risk-reducing salpingo-oophorectomy; AWD, alive with disease; NED, no evidence of disease; PPC, primary peritoneal carcinoma; pt, patient