Case Report

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Unusual Pattern of Spread of High-Grade Serous Fallopian Tubal Carcinoma in a Woman with *BRCA1* Gene Mutation

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ABSTRACT

A 40-year-old woman presented with chronic watery vaginal discharge for one-month and right pelvic pain radiating to the right flank for 2 weeks. Physical and pelvic examination revealed a right pelvic mass. Computerized tomography and magnetic resonance of whole abdomen revealed a 6-cm of heterogeneous mass at the right adnexa and a larger mass of 8-cm with internal cystic portions compressing on the inferior vena cava. Her serum cancer antigen (CA) 125 elevated to 540 U/ml. Surgical intervention revealed a right fallopian tube mass with an intact serosal surface, several enlarged pelvic and para-aortic nodes, and a bulky precaval node. No gross peritoneal nor other organ invasion was found. Complete surgical staging was performed by gynecologic oncologists and a surgeon, resulting in optimal surgery. Pathology revealed high-grade serous carcinoma of the right fallopian tube with metastasis to all resected nodes and a positive peritoneal cytology. Subsequent blood testing showed *BReast CAncer* (*BRCA*) 1 gene mutation. Adjuvant therapy with paclitaxel/carboplatin/bevacizumab was given for six cycles. Maintenance therapy with bevacizumab/olaparib, and periodic surveillance for other cancers, including breast magnetic resonance imaging were planned. This case presented an unusual pattern fallopian tubal cancer spread to a large precaval lymph node which was bulkier than the primary tumor. A thorough pre-operative evaluation and a surgical team specialized in cancer surgery are crucial for successful surgical management. Appropriate adjuvant treatment and follow-up for a woman with *BRCA* mutation were also to be emphasized.

KEYWORDS: BRCA gene mutation, fallopian tubal carcinoma, nodal metastasis

INTRODUCTION

Fallopian tubal carcinoma (FTCA) represents a rare gynecologic cancer frequently presented by a peritoneal spread that involves the ipsilateral ovary and other pelvic tissues, including the peritoneum. Small or early-stage FTCA may be asymptomatic until it ruptures through the serosa and spreads to the peritoneum and other viscera[1,2]. Most FTCA are diagnosed at an advanced stage, which causes difficulty in tracking its primary site and its misdiagnosis as the more common ovarian cancer[1,3].

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A FTCA limited to the primary location without gross invasion of the pelvic viscera and peritoneum but with distant nodal metastasis is rarely observed[4].

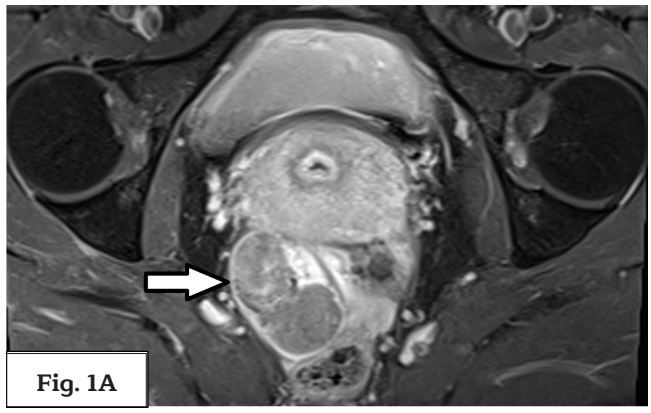
BReast CAncer (*BRCA*) gene is a tumor suppressor gene which produces proteins crucial for repair of damaged DNA. The *BRCA* gene is inherited from the parent, so-called germ line mutation. Its mutation can lead to uncontrolled cell growth contributing to the development of various cancers, especially breast and ovarian cancers[5-8]. In addition, these individuals may develop cancer at young ages[9].

CASE REPORT

A 40-year-old married Thai woman with parity 0, presented at the initial hospital for a right pelvic pain radiating to the right flank in the past 2 weeks. Pelvic examination discovered a right adnexal mass without other abnormal findings. Computerized tomography scan of the whole-abdomen revealed a heterogeneous enhancing mass at the right adnexa and a large well-defined heterogenous enhancing mass was detected compressing on the inferior vena cava without a fat plane, along with several para-aortic and pelvic nodes. Pertinent laboratory finding was an elevated CA125 to 540 U/ml. The patient self-referred to our hospital for treatment.

Additional history taking revealed the patient had stopped oral contraceptive pills for 5 years after her 10-year use. A recent breast surveillance involving mammogram and ultrasound was Breast Imaging-Reporting and Data System 3. Family history revealed several cancers in many family members: lung cancer in her father (also pancreatic and prostatic cancers) and brother; ovarian cancer in her sister whose daughter and son had breast and lung cancers, respectively; brain tumor in her auntie (maternal side) whose her daughter had breast cancer.

Magnetic resonance imaging (MRI) of abdomen was additionally performed to have detailed imaging for surgical planning. The right adnexal mass measuring 6.1x3.0x4.2 cm^3 was seen (figure 1A) discrete from the normal right ovary, right pelvic nodes sized up to 1.1 cm, a 3.2 cm, left ovarian cyst with septation and turbid content, and absence of ascites or peritoneal nodule. A 3.2x4.5x7.8 cm^3 well-defined heterogenous enhancing mass at precaval compressing on the inferior vena cava without a fat plane (figure 1B) and other para-aortic nodes with sizes ranging between 2-3 cm. Differential diagnoses of the right adnexal mass and bulky precaval node included pelvic soft tissue tumor and lymphadenopathy or primary retroperitoneal tumors.



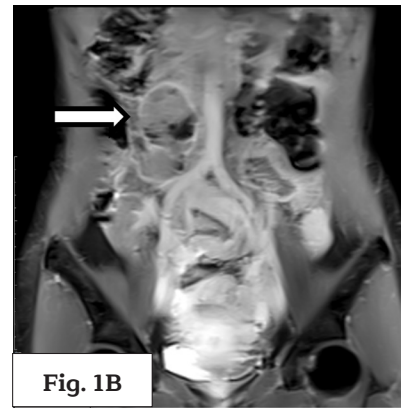


Figure 1 MRI images of lower abdomen revealed a 6.1×3.0×4.2 cm heterogenous enhancing mass at right adnexa abutting to right uterus, urinary bladder, and upper rectum without definite invasion (figure 1A). The image of upper abdomen showed a 4.5×4.0×8.4 cm lobulated mass with internal cystic portions compressing on inferior vena cava without fat plane (figure 1B).

Exploratory laparotomy revealed a right tubal mass measuring approximately 5 cm with a smooth serosal surface (figure 2A), a yellowish tan solid with foci of the hemorrhage cut surface (figure 2B), several enlarged right external iliac and para-aortic nodes with sizes up to 2.5 cm, and a large 8-cm precaval node with intact capsule (figure 2C). The cut surface of the large precaval node unveiled a homogeneous pinkish tan with foci of necrosis (figure 2D).

The right tubal mass and ovary were resected, followed by peritoneal washing, total hysterectomy, and left salpingo-oophorectomy. Resection of the large precaval nodes and other grossly enlarged para-aortic and pelvic nodes were also performed without bleaching of the nodal capsules. The tubal mass and precaval node were submitted for frozen section study which revealed the same features of high-grade carcinoma. Optimal surgery was achieved with an uneventful postoperative clinical outcomes.

The final pathology indicated a high-grade serous carcinoma of the right fallopian tube, with lymphatic invasion, metastasis to pelvic and para-aortic lymph nodes (4/18 nodes), and positive peritoneal washing. No evidence of cancer was found in both ovaries.

Blood germline test revealed *BRCA*1 gene mutation. Comprehensive genetic molecular profiling (CARIS Life Sciences' Molecular Intelligence platform) of the formalin-fixed paraffin-embedded tumor specimens was performed for analysis, and the results revealed the *BRCA*1 exon16 p.T1691K (likely pathogenic variant), TP53 exon4 (pathogenic variant), stable microsatellite instability, low tumor mutational burden (5 Mb), and high Homologous Recombinant Deficiency Genomic Scare (score of 60).

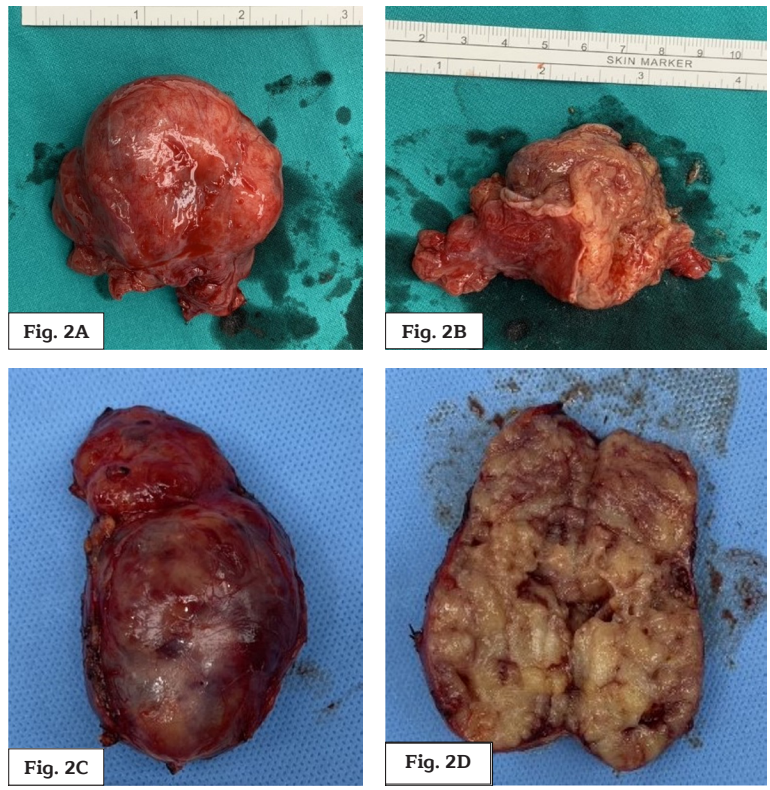


Figure 2 Gross finding of right tubal mass showed with intact serosa (figure 2A). Cut surface showed yellowish tan solid with foci of hemorrhage (figure 2B). Gross pathology of the large oval shape pre-caval lymph node measured 8.0×4.2×3.3 cm with smooth intact capsular surface (figure 2C). Cut surface revealed homogeneous pinkish tan with foci of necrosis (figure 2D).

The final diagnosis was high-grade serous carcinoma of right FTCA, stage IIIA1(ii) according to the 2021 International Federation of Gynecology and Obstetrics (FIGO 2021) in the young woman with *BRCA1* gene mutation.

Post-operative additional history taken revealed a 1-month watery vaginal discharge experienced by the patient. Her primary gynecologist deemed the discharge as normal, which prompted the patient to omit such information during our initial history-taking session.

The patient and her family were counseled about clinical and surgico-pathological findings, diagnoses, and treatment planning which included adjuvant therapy with paclitaxel/carboplatin/bevacizumab for six cycles followed by maintenance therapy with bevacizumab/olaparib. Periodic surveillance through interval breast MRI was also planned with consideration for prophylactic bilateral mastectomy.

She was currently doing well with no evidence of disease after 6 cycles of adjuvant therapy. Subsequent maintenance therapy was to be initiated. Taking into consideration her psychological state of adjustment for medical problems, a prophylactic mastectomy as a risk-reducing surgery will be delayed after a remission from fallopian tubal cancer.

DISCUSSION

FTCA occurs rarely, especially when compared with the more common ovarian cancer. Given its low prevalence and the presence of subtle nonspecific symptoms, a correct preoperative diagnosis presents a challenge, with only 4% (0.3%–15%) of cases being accurately diagnosed prior to surgery[1,10]. For the same reasons, FTCA often remains undetected until it ruptures through the serosa and spreads throughout the abdomen and pelvic cavity. At our best, we could not find any previous report of fallopian tube carcinoma which had bulkier metastatic node to upper abdomen than the primary tumor which was limiting within the tube.

Upon a retrospective review, our patient had all three clinical presentations meeting Latzko's triad of a FTCA, namely, watery vaginal discharge, colicky lower abdominal pain, and a pelvic mass, which can be observed in less than 15% of cases[11-13]. However, the patient's primary gynecologist regarded the reported watery discharge as not clinically meaningful. Thus, the patient skipped reporting such information during our initial history taking. We additionally performed MRI of whole abdomen in our hospital to evaluate the nature of the pelvic and precaval masses and their anatomical relationship with adjacent organs, which was crucial for accurate preoperative planning. The right ovary, which had not been visible on the CT scan, was identified from the MRI images. Additionally, the MRI provided a clear delineation of the precaval masses, even in the absence of a fat plane, thereby increasing our confidence in performing a successful surgical removal.

The resected right fallopian tube mass and pre-caval node were sent for an intraoperative frozen section to confirm its malignancy status, type, and their similar or distinctive features. This step was taken due to the unusual presence of a bulky metastatic node in the upper abdomen, despite limiting cancer spread in the pelvis.

The most frequent route of FTCA spread was through the serosal surface into the peritoneal viscera, especially the adjacent ipsilateral ovary and to other pelvic organs[2]. The clinical and surgico-pathological findings in our patient were unusual. This finding was observed possibly because the tumor (seemingly in early stage) had not yet breached the serosal surface. The positive peritoneal cytology was probably due to the spillage of tumor cells through the tubal fimbriae. The aggressive-behavior–high-grade serous carcinoma and lymphatic invasion around the primary tumor site may explain the unusual nodal spread to the para-aortic and precaval nodes in the upper abdomen.

Advanced ovarian cancer or FTCA necessitates a multidisciplinary approach that aims for a maximal tumor debulking and its favorable prognosis[4]. Our surgical team comprised two gynecologic oncologists and a surgeon. A meticulous approach was implemented to prevent/minimize the risk of tumor spillage, particularly in case of localized tumors, and ensure the safe resection of all enlarged nodes, including the bulky precaval node. As a result, the primary fallopian tubal tumor and lymph nodes, which had no gross invasion to the serosal or capsular surfaces, were removed intact.

Regarding the *BRCA* gene mutation, individuals with mutation show a high risk for several cancers compared with the general population. Compared with the lifetime risks of general women for developing breast or ovarian/fallopian tubal/peritoneal cancers (13% and 1.2%, respectively)[14], those who inherited the *BRCA1* gene mutation have 55%–72% and 39%–44% chances of developing these cancers by 70–80 years old[14-17].

The prevalence of *BRCA* gene mutation varies among various ethnic groups, characteristics, and personal/family history of the population studied. Among Asian population, data of *BRCA* gene mutation were more available for breast cancer. The prevalence of *BRCA* gene mutation ranged from 21.4 to 24.7%[18-20] or 14.6% for *BRCA1* and 23% for *BRCA*2 mutations[21,22]. The prevalence was found higher among the women with risk factors, such as, women with family history of breast/ovarian cancers, aged < 35 years, bilateral breast cancer, women with breast and ovarian cancer, and those with multiple risk factors[23-25].

Data on Asian population, especially ovarian cancer patients, are limited. Two studies in Thailand reported the prevalence of *BRCA* gene mutation in ovarian/FTCA and peritoneal cancers[26,27]. One research used either blood formalin-fixed paraffin-embedded tissue or a fresh tumor specimen and reported a 21.8% prevalence of germline *BRCA* mutation in cancer patients with high-grade histological tumors: 16.1% of *BRCA1* and 5.7% of *BRCA2* gene mutation[26]. A higher mutation rate was observed among patients with positive family history of breast/ovarian cancer and personal history of breast cancer. Patients with FTCA (60%) presented a higher frequency of *BRCA* mutation, followed by those with peritoneal cancer (50%) and epithelial ovarian cancer (18.2%). Notably, all cases with *BRCA* mutation had high-grade serous histopathology. Another study that used 139 tissue paraffin blocks reported a less than 10% of *BRCA* gene mutation in Thai ovarian cancer patients, being somatic mutation in 6.5% and germline mutation in 8.7% (from additional blood testing)[27]. The *BRCA* gene mutation was exclusively found in serous (30.0%) or clear-cell (5.8%) carcinoma.

Tests for inherited *BRCA1* and *BRCA2* variants may be completed using a blood, saliva, or tumor tissue sample. However, the *BRCA* gene mutation identified from tumoral tissue may be of somatic or germline origin, and thus, further blood testing is still required[28]. We performed genetic blood testing of *BRCA1* gene mutation according to the recommendation of the American Society of Clinical Oncology, which specifically states that all women diagnosed with epithelial ovarian cancer should undergo genetic testing for inherited *BRCA1*, *BRCA2*, and other ovarian cancer susceptibility genes, regardless of the clinical features of their disease or family history[29]. Furthermore, the need for genetic testing of the patient was underscored by the reporting of several types of cancer experienced by the patient's family members, in accordance with the criteria for genetic testing of the National Comprehensive Cancer Network, individuals who have a blood relative with a known or possibly has these genes, who certain personal and/or family histories of cancer, cancer diagnosed at a younger age, suffering from certain types of cancer, two or more cancer diagnoses, or families with multiple cases of cancer[30].

CONCLUSION

Our young patient, who carried *BRCA1* gene mutation, was diagnosed with high-grade serous carcinoma of the fallopian tube. The cancer spread to para-aortic lymph nodes as bulky masses, despite the localized primary tumor, was unusual. This case highlights the need for gynecologists or gynecologic oncologists to be aware of this possible event in ovarian/fallopian tubal cancer, especially high-grade serous carcinoma. Optimal surgical debulking of all gross tumors by experienced gynecologic oncologists and an expert surgeon was achieved without bleaching serosa of the primary tumor and metastatic nodal capsules. Emphasis should be placed on meticulous preoperative planning and intraoperative surgical management to ensure successful outcomes. Guidelines for management of an individual who had *BRCA* gene mutations should be followed, including maintenance targeted therapy after adjuvant chemotherapy and periodic history assessments and surveillance for other cancers.

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REFERENCES

1. Lau HY, Chen YJ, Yen MS, Chen RF, Yeh SO, Twu NF. Primary fallopian tube carcinoma: a clinicopathologic analysis and literature review. J Chin Med Assoc 2013;76(10):583-7.
2. Kalampokas E, Kalampokas T, Tourountous I. Primary fallopian tube carcinoma. Eur J Obstet Gynecol Reprod Biol 2013;169(2): 155-61.
3. Kalampokas E, Sofoudis C, Boutas I, Kalampokas T, Tourountous I. Primary fallopian tube carcinoma: a case report and mini-review of the literature. Eur J Gynaecol Oncol 2014;35(5):595-6.
4. Borghese M, Vizzielli G, Capelli G, Santoro A, Angelico G, Arciuolo D, et al. Retrospective study of histopathological and prognostic characteristics of primary fallopian tube carcinomas: twenty-year experience (SOCRATE). Int J Gynecol Cancer 2022: ijgc-2022-003468.
5. Paul A, Paul S. The breast cancer susceptibility genes (BRCA) in breast and ovarian cancers. Front Biosci (Landmark Ed) 2014;19(4):605-18.
6. Kroeger PT Jr, Drapkin R. Pathogenesis and heterogeneity of ovarian cancer. Curr Opin Obstet Gynecol 2017;29(1):26-34.
7. Loboda AP, Adonin LS, Zvereva SD, Guschin DY, Korneenko TV, Telegina AV, et al. BRCA mutations-the achilles heel of breast, ovarian and other epithelial cancers. Int J Mol Sci 2023;24(5):4982.
8. Petrucelli N, Daly MB, Feldman GL. Hereditary breast and ovarian cancer due to mutations in BRCA1 and BRCA2. Genet Med 2010;12(5):245-59.
9. Young AL, Butow PN, Vetsch J, Quinn VF, Patenaude AF, Tucker KM, et al. Family communication, risk perception and cancer knowledge of young adults from BRCA1/2 families: a systematic review. J Genet Couns 2017;26(6):1179-96.
10. Ajithkumar TV, Minimole AL, John MM, Ashokkumar OS. Primary fallopian tube carcinoma. Obstet Gynecol Surv 2005;60(4): 247-52.
11. Lawson F, Lees C, Kelleher C. Progress in obstet and gynecol. In: Studd J, editor. Primary cancer of fallopian tube. London: Churchill Livingstone; 1996. p. 393–401.
12. Vyas MN, Rai S, Manjeera L, Shetty D. Bilateral primary fallopian tube carcinoma with the classical clinical features: a case report. J Clin Diagn Res 2013;7(4):726-8.
13. Bao L, Ding Y, Cai Q, Ning Y, Hu W, Xue X, et al. Primary fallopian tube carcinoma: a single-institution experience of 101 cases: a retrospective study. Int J Gynecol Cancer 2016;26(3):424-30.

14. chenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 2017;317:2402-16.
15. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. Am J Hum Genet 2003;72(5):1117-30.
16. Chen S, Parmigiani G. Meta-analysis of BRCA1 and BRCA2 penetrance. J Clin Oncol 2007; 25(11):1329-33.
17. Finch A, Beiner M, Lubinski J, Lynch HT, Moller P, Rosen B, et al. Salpingo-oophorectomy and the risk of ovarian, fallopian tube, and peritoneal cancers in women with a BRCA1 or BRCA2 Mutation. JAMA 2006;296(2):185-92.
18. Kumar BV, Lakhotia S, Ankathil R, Madhavan J, Jayaprakash PG, Nair MK, et al. Germline BRCA1 mutation analysis in Indian breast/ ovarian cancer families. Cancer Biol Ther 2002;1(1):18-21.
19. Saxena S, Szabo CI, Chopin S, Barjhoux L, Sinilnikova O, Lenoir G, et al. BRCA1 and BRCA2 in Indian breast cancer patients. Hum Mutat 2002;20(6):473-4.
20. Rashid MU, Muhammad N, Naeemi H, Khan FA, Hassan M, Faisal S, et al. Spectrum and prevalence of *BRCA1/2* germline mutations in Pakistani breast cancer patients: results from a large comprehensive study. Hered Cancer Clin Pract 2019;17:27.
21. De Silva W, Karunanayake EH, Tennekoon KH, Allen M, Amarasinghe I, Angunawala P, et al. Novel sequence variants and a high frequency of recurrent polymorphisms in BRCA1 gene in Sri Lankan breast cancer patients and at risk individuals. BMC Cancer 2008;8:214.
22. De Silva S, Tennekoon KH, Dissanayake A, De Silva K, Jayasekara L. Novel and reported pathogenic variants in exon 11 of BRCA2 gene in a cohort of Sri Lankan young breast cancer patients. Fam Cancer 2017;16(3): 329-38.
23. Kang E, Seong MW, Park SK, Lee JW, Lee J, Kim LS, et al. The prevalence and spectrum of BRCA1 and BRCA2 mutations in Korean population: recent update of the Korean Hereditary Breast Cancer (KOHBRA) study. Breast Cancer Res Treat 2015;151(1):157-68.
24. Han SA, Kim SW, Kang E, Park SK, Ahn SH, Lee MH, et al. The prevalence of BRCA mutations among familial breast cancer patients in Korea: results of the Korean Hereditary Breast Cancer study. Fam Cancer 2013;12(1):75-81.
25. Lang GT, Shi JX, Hu X, Zhang CH, Shan L, Song CG, et al. The spectrum of BRCA mutations and characteristics of BRCA-associated breast cancers in China: screening of 2,991 patients and 1,043 controls by next-generation sequencing. Int J Cancer;141(1):129-42.
26. Manchana T, Phoolcharoen N, Tantbirojn P. *BRCA* mutation in high grade epithelial ovarian cancers. Gynecol Oncol Rep 2019;29:102-5.
27. Lertkhachonsuk AA, Suprasert P, Manchana T, Kittisiam T, Kantathavorn N, Chansoon T, et al. Prevalence of tissue BRCA gene mutation in ovarian, fallopian tube, and primary peritoneal cancers: a multi-institutional study. Asian Pac J Cancer Prev 2020;21(8):2381-8.
28. Gajda-Walczak A, Potęga A, Kowalczyk A, Sek S, Zięba S, Kowalik A, et al. New, fast and cheap prediction tests for BRCA1 gene mutations identification in clinical samples. Sci Rep 2023;13(1):7316.
29. Konstantinopoulos PA, Norquist B, Lacchetti C, Armstrong D, Grisham RN, Goodfellow PJ, et al. Germline and somatic tumor testing in epithelial ovarian cancer: ASCO guideline. J Clin Oncol 2020;38(11):1222-45.
30. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: genetic/familial high-risk assessment: breast, ovarian, and pancreatic. Plymouth: National Comprehensive Cancer Network; 2020.