

# High-grade serous ovarian cancer 3 years after bilateral salpingectomy: A case report

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**Abstract.** Although epithelial ovarian cancer commonly originates from the ovarian surface epithelium and/or ovarian inclusion cysts, it was recently proposed that high-grade serous ovarian cancer (HGSC) develops from the Fallopian tubes. In our department, we encountered a case of HGSC that contradicts the hypothesis of a tubal origin for HGSC. A 51-year-old postmenopausal woman had undergone hysterectomy, left oophorectomy and bilateral salpingectomy for uterine myoma. Three years later, the patient was diagnosed with stage IV ovarian cancer and underwent primary debulking surgery. The pathological examination revealed HGSC, although there was no evidence of serous tubal intraepithelial carcinoma or any other type of cancer in the previously resected left ovary and bilateral Fallopian tubes. Moreover, p53 overexpression was not detected in the right ovarian cancer specimen, while paired box gene 8, a marker of Fallopian tube epithelium, was highly expressed. Therefore, HGSC may develop from an inclusion cyst with metaplasia of from the ovarian surface epithelium.

## Introduction

Serous epithelial ovarian cancer (EOC) accounts for ~75% of EOC subtypes (1,2). The majority of patients with EOC have no identifiable risk factors or precursor lesions, and only few effective screening tools for early diagnosis are currently available (3).

EOC commonly originates from the ovarian surface epithelium (OSE) and/or ovarian inclusion cysts (4,5). However, an American pathology group recently proposed a novel hypothesis, that high-grade serous ovarian cancer (HGSC) (6), the most common histological subtype of EOC,

develops from the Fallopian tubes. Moreover, previous studies reported that salpingectomy may be associated with a reduced risk of ovarian cancer, particularly serous EOC (4,6,7). However, this hypothesis does not yet have an adequate scientific basis. We herein report a case of HGSC that developed 3 years after bilateral salpingectomy (BS), which contradicts the hypothesis of a tubal origin for HGSC.

## Case report

A 51-year-old postmenopausal woman presented to the Department of Obstetrics and Gynecology of Shimane University Hospital (Izumo, Japan) on July, 2014 with low abdominal distention. The patient had a history of uterine myoma and had undergone total abdominal hysterectomy, left oophorectomy and BS 3 years prior. The patient was referred to our hospital from her primary care provider for suspected ovarian cancer. Marked ascites and a palpable mass were detected in the right adnexal region. The serum carbohydrate antigen-125 levels were elevated to 604 ng/ml (normal, <35 U/ml). Magnetic resonance imaging revealed ascites and a mass ~8 cm in diameter in the right adnexal region (Fig. 1). Positron emission tomography-computed tomography revealed peritoneal dissemination, omental cake and para-aortic lymph node metastasis (Fig. 2).

The patient underwent primary debulking surgery (right oophorectomy, omentectomy and resection of disseminated nodules). Pathological examination revealed stage IV (International Federation of Gynecology and Obstetrics 1988 guidelines) grade 2 ovarian serous adenocarcinoma, with right pleural metastasis, liver surface metastasis and peritoneal dissemination. A large number of residual tumors were sized >2 cm. As adjuvant therapy, the patient received combination chemotherapy with paclitaxel (175 mg/m<sup>2</sup>), carboplatin (area under the curve = 5) and bevacizumab (15 mg/kg) (Fig. 3) [Specifically, the patient received paclitaxel (Taxol)-carboplatin (Carbo) plus bevacizumab (TC+BEV) therapy triweekly, for six cycles; BEV monotherapy as a maintenance therapy, triweekly for 16 cycles; at the progression stage of the disease, 16 months after adjuvant TC therapy+BEV, with the growth of intra-peritoneal implantations, the patient received TC+BEV triweekly, for six cycles), and subsequently BEV monotherapy (triweekly; now, the patient receives 1 cycle, and she has stable disease].

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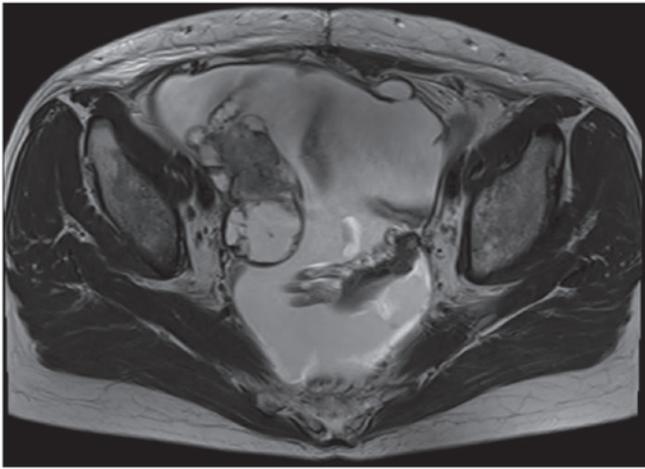


Figure 1. Preoperative axial T2-weighted magnetic resonance imaging revealed a mass sized 84 mm in the right adnexal region, as well as ascites.

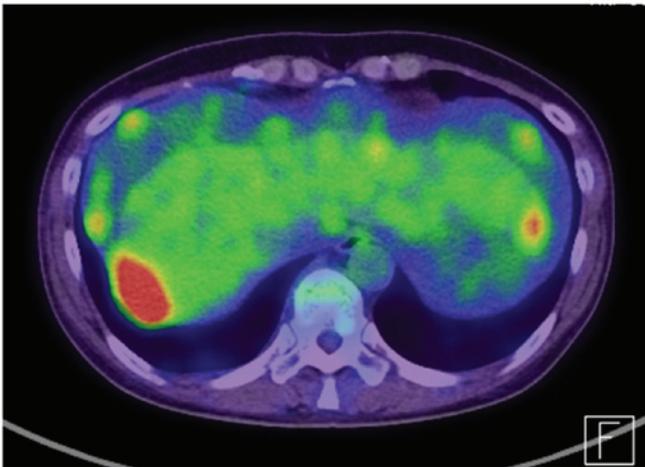


Figure 2. Preoperative positron emission tomography-computed tomography imaging revealed peritoneal dissemination, omental cake and para-aortic lymph node metastases.

Immunohistochemical examination revealed that p53 was not overexpressed in the tumors or in the inclusion cyst of the OSE. However, paired box gene 8 (PAX8), a marker of Fallopian tube epithelium, was strongly positive in the bilateral Fallopian tubes and the tumor cells, while it was not expressed in the inclusion cyst of the OSE. The previously resected left ovary was examined, and although there was no evidence of serous tubal intraepithelial carcinoma (STIC) or any other cancer, PAX8-positive cells were detected (Fig. 4).

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

## Discussion

HGSC is the most common histological subtype of EOC and it was previously hypothesized that the risk reduction observed among women who undergo BS mainly reflects a lower incidence of HGSC (4). Previous findings support the theory of ovarian cancer originating in the Fallopian

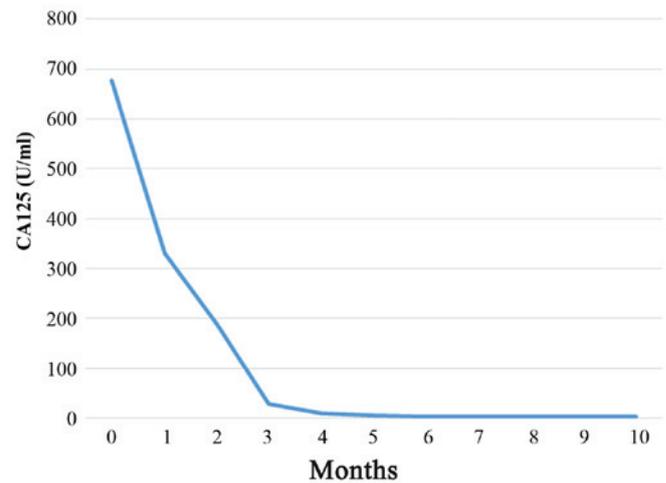


Figure 3. The serum levels of the tumor marker CA125 decreased over the course of adjuvant treatment with paclitaxel (Taxol)-carboplatin (Carbo) plus bevacizumab (TC+BEV) therapy, indicating response to treatment. CA, carbohydrate antigen.

tubes (4,6,7). However, data from observational studies are generally limited by small sample size, hospital-based study populations, insufficient control regarding the effects of oophorectomy, or the influence of time from a bilateral salpingectomy to the formation of ovarian cancer (4).

Studies emerging from The Cancer Genome Atlas Research Network have shed some light on the genetics of ovarian cancer (4,8,9). HGSC is commonly driven by p53 and breast cancer, early onset (BRCA) gene mutations (4). Morphological studies of the Fallopian tubes in BRCA mutation carriers have also been identified the STIC region (10). Therefore, if HGSC develops from the Fallopian tubes, it is likely that the STIC region and/or p53 mutations are present. The association between STIC and the p53 signature has not yet been investigated in HGSC.

To date, it has been hypothesized that STIC lesions are shed through the Fallopian tubes and incorporated into ovarian surface inclusion cysts, where they subsequently transform into HGSC, and are associated with an activating p53 mutation. In the present case, STIC or p53 overexpression were not detected, which may overturn the theory that ovarian cancer, particularly HGSC, originates in the Fallopian tubes. Based on these findings, we consider that other mechanisms may be associated with HGSC development in patients without p53 mutations. In the present case, we hypothesize that HGSC may have originated from an inclusion cyst of OSE or an inclusion cyst of the tubal epithelium, without STIC reaching the surface of the ovary, as previously reported (11).

However, PAX8, a marker of Fallopian tube epithelium, was strongly expressed in the bilateral Fallopian tubes and in the tumor cells. We are currently investigating the frequency of PAX8-positive cells in ovarian cancer in an attempt to elucidate its role in ovarian carcinogenesis.

In conclusion, we herein report a case of HGSC that developed 3 years after BS, contradicting the hypothesis of a tubal origin. There was also no region of STIC or p53 expression detected in the present case. Based on these findings, we consider that other mechanisms must be responsible for carcinogenesis in HGSC in patients without p53 mutations.

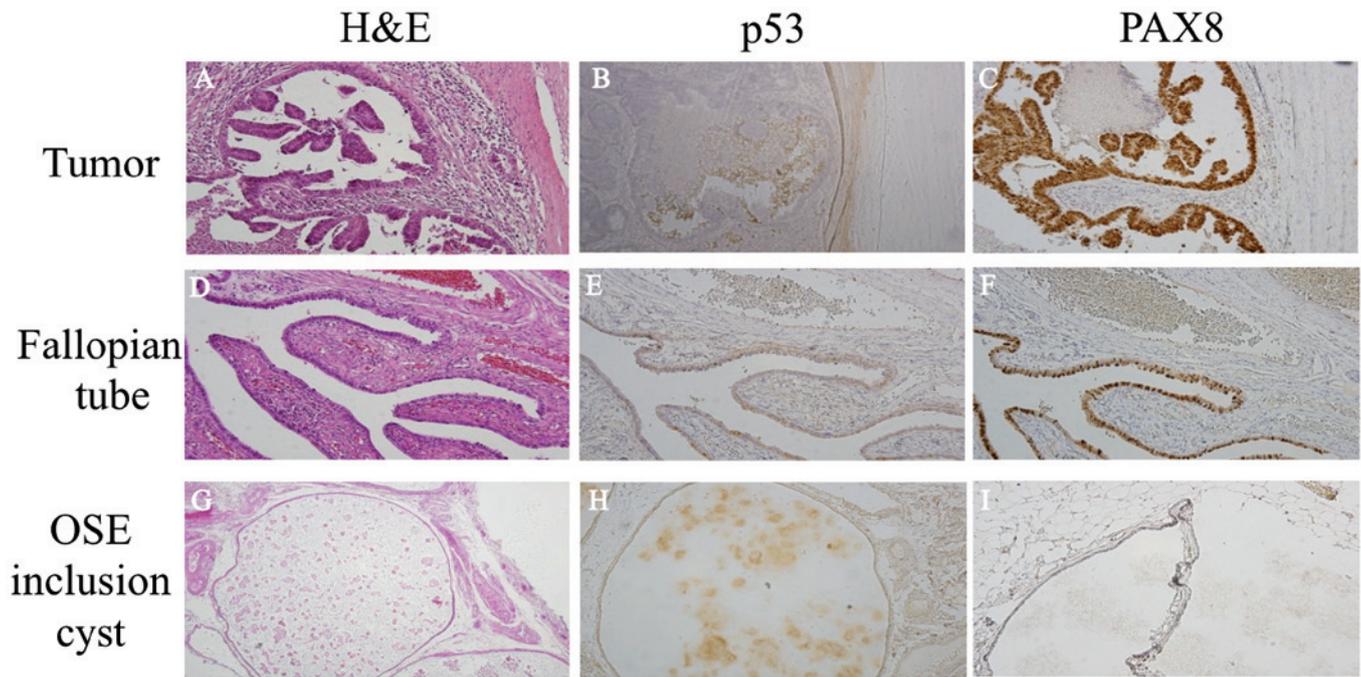


Figure 4. Immunohistochemical images of the tumor, Fallopian tubes (resected 3 years prior) and inclusion cyst of OSE. Tumor samples were collected from the right ovary. OSE inclusion cysts were obtained from the right ovary. p53 was moderately expressed in the tumor (1+), Fallopian tubes (1+) and the inclusion cyst of the OSE (1+). PAX8 was highly expressed in the Fallopian tubes (3+) and tumor cells (3+). Magnification of all the images (A-I), x40. PAX8, paired box gene 8; H&E, hematoxylin and eosin; OSE, ovarian surface epithelium.

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