Serous Tubal Intraepithelial Carcinoma in a Japanese Woman with a Deleterious BRCA1 Mutation

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Risk-reducing salpingo-oophorectomy for reducing future cancer risk in women with hereditary breast and ovarian cancer syndrome is rarely performed in Japan; therefore, the cancer preventive effect of risk-reducing salpingo-oophorectomy for hereditary breast and ovarian cancer syndrome among the Japanese population remains unclear. Here, we report the first case of serous tubal intraepithelial carcinoma identified through a risk-reducing salpingo-oophorectomy in a Japanese woman with hereditary breast and ovarian cancer syndrome and who had a deleterious germline mutation of E1214X in BRCA1, but not a BRCA2 mutation. A pre-operative examination revealed multiple uterine leiomyomas but no adnexal mass. Robotic-assisted bilateral salpingo-oophorectomy together with hysterectomy was performed. A pathological examination identified serous tubal intraepithelial carcinoma in the right fallopian tube with no dissemination. Serous tubal intraepithelial carcinoma is implicated as an origin of invasive cancer of the fallopian tube with peritoneal dissemination; prophylactic salpingo-oophorectomy is currently the only method to identify this occult cancer. Our case demonstrated that risk-reducing salpingo-oophorectomy can detect occult cancers, including serous tubal intraepithelial carcinoma, thereby preventing future cancer development in the Japanese hereditary breast and ovarian cancer syndrome population.

Key words: BRCA1 — hereditary breast and ovarian cancer syndrome — fallopian tube neoplasm — genetic counseling

INTRODUCTION

In Japan, the number of women seeking genetic screening for hereditary breast and ovarian cancer syndrome (HBOC) has been increasing; however, it remains difficult for several patients to receive adequate information on familial cancers because of the lack of a systematic genetic counseling system and adequate coverage by the national health insurance system (1,2). Widely recognized genetic risk factors for HBOC include germline mutations in the tumor suppressor breast cancer 1, early onset (BRCA1) and/or breast cancer 2, early onset (BRCA2). Inherited deleterious mutations in BRCA1 and/or BRCA2 confer an increased lifetime risk of developing breast and ovarian cancer (3). Mutations in BRCA1 are responsible for ~40% inherited breast cancers and >80% inherited breast and ovarian cancers in the USA. The risk of developing breast and ovarian cancer associated with BRCA1 mutations increases to over 70 and 50%, respectively, by the age of 70 in the United States (4); however, the same risks for developing breast and ovarian cancer remain unknown in Japan.

Risk-reducing salpingo-oophorectomy (RSO) is defined as the excision of non-neoplastic ovaries and fallopian tubes to reduce the risk of familial breast cancer and future cancers,
arising from the reproductive organs. In western countries, RRSO is a recognized cancer prevention strategy for women with HBOC who carry germline \( \text{BRCA1} \) and/or \( \text{BRCA2} \) mutations (5). RRSO is generally recommended to women who have a \( \text{BRCA1}/\text{BRCA2} \) mutation by the age of 35 years or after child-bearing age because most ovarian and tubal cancers are detected in advanced states, despite annual gynecological examinations (6,7).

Atypical epithelial lesions and serous intraepithelial carcinoma of the fallopian tubes, which is also known as serous tubal intraepithelial carcinoma (STIC), is sometimes pathologically detected in RRSO specimens (8). STIC is considered as a precursor of invasive tubal serous carcinoma with a broad range of peritoneal dissemination (9,10). However, preoperative early recognition of STIC is nearly impossible because most cases are asymptomatic; therefore, the only opportunity to detect STIC and other occult cancers arising from the ovary and tube is RRSO with an extensive pathological examination. Several reports have revealed the existence of occult cancers in young women with \( \text{BRCA1}/\text{BRCA2} \) mutations in western countries (11–13); however, the prevalence of these occult cancers in Japanese women with \( \text{BRCA1}/\text{BRCA2} \) mutations remains unclear, partly because of the low incidence of RRSO.

Here we report a case of STIC identified at RRSO together with hysterectomy in a post-menopausal Japanese woman with a deleterious germline \( \text{BRCA1} \) mutation. Although no neoplastic lesions were detected in either ovary or fallopian tube at the initial gynecological examination, the patient preferred RRSO including hysterectomy after adequate genetic counseling. We believe that this is the first case of STIC identified in a disease-free Japanese woman with asymptomatic HBOC.

**CASE REPORT**

A 51-year-old post-menopausal woman was admitted to our facility for genetic counseling on hereditary familial cancer syndrome. Her father had died of colorectal cancer, and her mother had died of ovarian cancer at the age of 51 years. The patient acted as a surrogate healthcare provider for her mother when she was a high school student and was present when her mother died. A medical history revealed several breast and ovarian cancer-related deaths in her maternal lineage (Fig. 1). Based on our client’s family history, she was initially afraid to undergo genetic screening for specific gene mutations related to familial cancer syndrome. After receiving sufficient information on HBOC through professional counseling, she agreed to be genetically screened for possible \( \text{BRCA1}/\text{BRCA2} \) mutations. Genetic analysis (provided by FALCO Biosystems, Inc. Japan) revealed a deleterious germline \( \text{BRCA1} \) nonsense mutation, E1214X; therefore, our client was given further information regarding the correlation between deleterious \( \text{BRCA1} \) mutations and the future risk of cancer development, cancer screening methods and modes of inheritance, after which she finally decided to undergo RRSO. An ultrasound examination revealed multiple uterine leiomyomas, some of which had an abundant blood supply by color Doppler imaging; however, no neoplastic ovarian or tubal lesions were detected. Cytological screening for the detection of uterine cancer was negative.

Because the patient was post-menopausal, she requested removal of her adnexa and uterus. Thus, we performed robotic-assisted bilateral salpingo-oophorectomy together with hysterectomy as an RRSO. We laparoscopically confirmed that neither ascites nor apparent tumor lesion was present in her peritoneal cavity; thus, we did not perform a peritoneal washing cytology during surgery. The patient’s post-operative progress was good, and she was discharged from the hospital 5 days after surgery. The resected uterus was \( 7.6 \times 6.0 \times 4.0 \) cm and weighted 69.2 g. Macroscopically, bilateral ovaries and tubes and the uterus were unremarkable, except for multiple nodular lesions in the uterine myometrium, the greatest diameter of which was 3.0 cm. A histological examination revealed small foci of atypical epithelial

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**Figure 1.** Pedigree of a proband individual with a \( \text{BRCA1} \) mutation. The arrow indicates outpatient (proband). The number represents age and the organ represents the site of cancer origin. Roman numerals on the left edge represent generations. P, proband; squares, males; circles, females; oblique line, deceased.
cell proliferation in the mucosa of the right tubal fimbria (Fig. 2). In those foci, the cells were highly atypical with a high nuclear/cytoplasmic ratio and lacked cilia (Fig. 3A). We easily identified mitosis in the foci. Although the cells were occasionally stratified and less cohesive, there was no indication of prominent papillary proliferation or stromal invasion; thus, we diagnosed the lesion as STIC. The tumor cells showed diffuse immunoreactivity for p53 (Fig. 3B). The nodular lesions of the uterine myometrium were confirmed as leiomyoma. On microscopic examination, we did not find any neoplastic lesions in the uterine cervix, endometrium, peritoneum, left tube or either ovary, including atypical endometrial hyperplasia and cervical intraepithelial neoplasia. Epithelial inclusion cysts were appreciated without any atypia on the surface of both ovaries.

After surgery, the patient continued breast cancer screening every 6 months and has been cancer-free for the past 2 years. She has two daughters, a 24-year-old and an 18-year-old, and is concerned about the possibility of their inheriting the familial deleterious BRCA1 mutation. She has recommended both her daughters to undergo screening for BRCA1 mutation and future genetic counseling.

DISCUSSION
To the best of our knowledge, this is the first report of STIC identified in RRSO specimens from a Japanese woman with a deleterious BRCA1 mutation. Although the exact prevalence of HBOC in the Japanese population remains unclear, our case indicated the existence of occult cancer including STIC in Japanese women, as in European and American women.

The recent surge in public interest regarding HBOC in Japan has caused a simultaneous increase in the demand for genetic screening for HBOC, Lynch syndrome and other familial cancer syndromes; however, the lack of nationwide data regarding the prevalence, penetrance and mutation status of BRCA1/2 in Japan makes it difficult to provide appropriate information on HBOC to potential clients. Recently, a Japanese group reported the prevalence and characteristics of BRCA1/2 in HBOC patients in a Japanese population: among 260 probable cases with a strong family history of breast cancer, 46 (17.7%) were positive for BRCA1 mutations and 35 (13.5%) for BRCA2 mutations. Most instances of BRCA1 mutations were triple negative breast cancer. A previous study concluded that the prevalence of HBOC in Japan was roughly similar to that in western countries (14). A retrospective analysis of 102 primary ovarian cancer patients, including nine cases of HBOC, revealed a correlation between a family history of ovarian cancer in Japanese women and BRCA1/2 mutations (15). Of six cases with deleterious BRCA1/2 mutations, the
histological tumor types were serous carcinoma in four and endometrioid carcinoma in two, and all were HBOC-related cancers within second-degree probands. In this report, the first case of occult cancer in the ovary identified during RRSO in a Japanese woman with a BRCA1 mutation is described. Cancer cells were detected on the ovarian surface, and p53 immunoreactivity was identified in the normal tubal epithelium and in cancer cells on the surface of the ovary.

In this case, we identified a deleterious nonsense mutation of BRCA1, E1214X. This mutation is classified as haplotype 1, which is the most common haplotype out of the 10 canonical BRCA1 haplotypes (16). Without functional BRCA, the cell is forced to repair the double-stranded DNA break through other mechanisms, which are error-prone, create instability and lead to mutations. This same mutation has already been identified in a Japanese HBOC case (14).

STIC is now recognized as a distinct precursor lesion of tubal and some pelvic high-grade serous carcinomas that were previously considered as ovarian, peritoneal or of unknown origin (11,17). STIC or other tubal intraepithelial neoplasms in RRSO are the earliest stage malignancies that are microscopically recognizable in HBOC patients. Complete resection of these occult lesions may prevent development of invasive cancer that leads to poor prognoses in HBOC patients. Although the exact prevalence of STIC and other occult cancer lesions in HBOC patients remains unclear in Japan, the coexistence of mucosal carcinoma of the fallopian tubes in Japanese ovarian cancer cases has been reported. For example, in a previous report, there were seven histologically confirmed cases of mucosal carcinoma of the fallopian tubes coexisting with serous carcinoma obtained from 52 invasive ovarian carcinoma and three peritoneal serous carcinoma specimens (18).

Undergoing hysterectomy in addition to RRSO allows for estrogen-only therapy to replace the sex steroid hormones without an increased risk of endometrial cancer (19). Laparoscopic or robotic-assisted salpingo-oophorectomy together with hysterectomy requires approximately the same size of incision and only a slightly increased surgical time compared with salpingo-oophorectomy alone. Most patients who desire RRSO have children and no desire for future pregnancies. Thus, simultaneous hysterectomy can be either laparoscopically or robotically added during RRSO. In the current case, we performed robotic-assisted bilateral salpingo-oophorectomy together with hysterectomy as an RRSO because the patient was post-menopausal and had an unusual leiomyoma nodule with an abundant blood supply as revealed by color Doppler ultrasound. We pathologically confirmed the absence of uterine neoplastic lesions other than a common leiomyoma nodule. Because most of the uterus appeared to be normal in size during RRSO, and detailed inspection by laparoscopy is useful for the detection of abnormal lesions in the pelvis, minimal invasive surgery such as laparoscopic or robotic-assisted surgery may be suitable.

Meta-analysis revealed that RRSO significantly reduced breast cancer risk in BRCA1/2 mutation carriers. In addition, RRSO reduced the risk of BRCA1/2-associated ovarian and tubal cancer (20). However, because of the low penetrance and recognition rate of HBOC, the importance of RRSO for the preventive treatment of HBOC remains largely unrecognized in Japan. The recent surge in public interest of HBOC has resulted in an increased demand for cancer genetic counseling and subsequent applicants for RRSO. Therefore, there is an urgent requirement to establish an adequate cancer genetic counseling system and accommodate subsequent RRSO for patients with HBOC in Japan (21). It is fascinating that another group established a system for performing RRSO for BRCA1/2 mutation carriers in Japan. In addition, it should be emphasized that an extensive pathological examination, particularly in the fimbriated end of the fallopian tube, is extremely important to identify intraepithelial and early invasive carcinomas (9,22).

In conclusion, the present report is the first to document a case of STIC identified at RRSO in a Japanese woman with HBOC. We recommend the establishment of an appropriate cancer genetic counseling system and RRSO to reduce future cancer risks for Japanese HBOC patients.

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Conflict of interest statement

None declared.

References