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News about serous ovarian Ca

To our surprise, it can begin in the fallopian tube

FAST TRACK

Serous "ovarian" cancer might begin in the distal fallopian tube, where *p53* mutations can be detected

CASE Woman elects risk-reducing pelvic surgery

A 47-year-old, G3P3 woman who has a strong family history of ovarian and breast cancer is known to carry a deleterious mutation in the BRCA1 gene. She elects risk-reducing pelvic surgery, and her primary gynecologist performs bilateral oophorectomy. The following year, the consulting oncologist reviews the operative note and realizes that the fallopian tubes were not removed.

How should this woman be counseled?

Salpingo-oophorectomy has preventive value

Women who are known to carry a deleterious mutation of the BRCA1 or BRCA2 gene are at high risk of breast, ovarian, fallopian tube, and peritoneal cancer. Because we are unable to detect pelvic serous cancer at an early stage, risk-reducing bilateral salpingo-oophorectomy (rrBSO) has been recommended as a method for preventing these cancers. The value of such surgery is proven: Among women at high risk, rrBSO decreases the risk of breast, ovarian, and fallopian tube cancer.[1,2]

The majority of women who test positive for BRCA1 and BRCA2 elect to undergo either rrBSO (after completing their childbearing) or mastectomy.[3] Removal of the fallopian tubes is a critically important aspect of the rrBSO procedure for these women at high risk because we are learning that **many serous cancers labeled "ovarian" appear to begin in the fimbriated portion of the fallopian tube.**

Research has been revelatory

We have learned a great deal from studies of BRCA-positive women in this area:

The fallopian tube may be the preferred site for serous tumors to arise (see "Evidence: Serous tumors show a predilection for the tube," on page 10).

***p53* mutations are detectable.** Molecular analyses of the fallopian tubes of women who have BRCA1 mutations have demonstrated that the fimbriated end of the tube—but not the proximal tube—have areas of *p53* mutations in secretory cells but not in ciliated cells.[4] The somatic *p53* mutations in the fallopian tube (in combination with the germ-line BRCA mutation) may be an important step on the pathway to cancer.

The twin observations that

1. the fimbriated portion of the fallopian tube harbors *p53* mutations and
2. intraepithelial lesions of the fallopian tube are present in some women who carry deleterious BRCA1 mutations

suggest that serous "ovarian" cancer might actually begin in the distal fallopian tube. The lesions may then metastasize to ovarian and peritoneal surfaces, where the microenvironment is especially conducive to the growth of tumor.

These observations raise the possibility that the biologic process leading to "ovarian" cancer involves significant interaction between tubal and ovarian epithelia.

2-mm serial sectioning is required

Oncologists only recently recognized that detecting occult fallopian tube and ovarian cancers in women at high risk requires meticulous serial sectioning of the

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Evidence: Serous tumors show a predilection for the tube

Several studies of BRCA-positive women have demonstrated that the fallopian tube has a central role in hosting tumors.

- In a series of 94 healthy women who were BRCA1-positive and underwent rrBSO, 6 cancers (6.4%) were detected.[1] Of those 6 cancers, 2 were present in the fallopian tube only, 3 were present in the tube and the ovary, and 1 was present in the ovary only.
- Other investigators have also reported that the fallopian tube may be the preferred site for origin of serous tumors in women who carry a deleterious mutation of BRCA1 or BRCA2. In 1 series of 58 BRCA1 carriers who underwent rrBSO, for example, occult cancer was detected in 5 women (8.6%), including 2 occult cancers involving the fallopian tube only, 2 cancers involving the ovary only, and 1 case involving the ovary and the tube.[2]
- In another series of 13 BRCA-positive women, 5 cancers were detected—all of which involved only the fallopian tube.[3] Two of the 5 fallopian tube lesions were invasive cancers; 3 were reported to be intraepithelial (noninvasive). Of note, among these 13 BRCA-positive women, the mean age of women with and without fallopian tube cancer was 58 and 45 years, respectively—suggesting that, among BRCA-positive women, the risk of developing pelvic cancer increases as the women age. Other studies have supported this finding.

1. Finch A, Shaw P, Rosen B, et al. Clinical and pathologic findings of prophylactic salpingo-oophorectomies in 159 BRCA1 and BRCA2 carriers. Gynecol Oncol. 2006;100:58–64.
2. Olivier RI, van Beurden M, Lubsen MAC, et al. Clinical outcome of prophylactic oophorectomy in BRCA1/BRCA2 mutation carriers and events during follow-up. Br J Cancer. 2004;90:1492–1497.
3. Medeiros F, Muto MG, Lee Y, et al. The tubal fimbria is a preferred site for early adenocarcinoma in women with familial ovarian cancer syndrome. Am J Surg Pathol. 2006;30:230–236.

entire fallopian tube and ovary at 2-mm intervals. Such histologic processing is far more rigorous than the standard approach to handling surgical specimens of the fallopian tubes and ovaries.[5] Unless serial sectioning is performed, many of these occult lesions remain undetected.

CASE Patient resubmits to surgery

In the case described at the beginning of this Editorial, the patient had her ovaries, but not her fallopian tubes, removed. Alone, bilateral oophorectomy decreased her risk of ovarian cancer and breast cancer (by curtailing production of ovarian hormones), but she remains at increased risk of fallopian tube and peritoneal carcinoma because she did not have her fallopian tubes removed. The patient is offered a second surgery to remove both fallopian tubes. She accepts this option.

What specific risk did the incomplete surgery pose to the patient? In 1 case series, among women at high risk of pelvic cancer, bilateral oophorectomy alone was associated with an 11.5% risk of peritoneal papillary serous carcinoma (PPSC) postoperatively. On the other hand, removing the ovaries and fallopian tubes was associated with no cases of PPSC.[6]

Most experts recommend that as much as possible of the fallopian tube be removed at surgery. Because most occult fallopian tube lesions have been reported in the fimbriated end of the tube, removing the interstitial portion is unnecessary. If surgical staging is indicated, it should be performed at surgery.

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4. Lee Y, Miron A, Drapkin R, et al. A candidate precursor to serous carcinoma that originates in the distal fallopian tube. J Pathol. 2007;211:26–35.
5. Powell CB, Kenley E, Chen LM, et al. Risk-reducing salpingo-oophorectomy in BRCA mutation carriers: role of serial sectioning in the detection of occult malignancy. J Clin Oncol. 2005;23:127–132.
6. Olivier RI, van Beurden M, Lubsen MAC, et al. Clinical outcome of prophylactic oophorectomy in BRCA1/BRCA2 mutation carriers and events during follow-up. Br J Cancer. 2004;90:1492–1497.