INTRODUCTION

Malignant tumors arising in the ovary, fallopian tube, and peritoneum are frightening to contemplate—unlike cervical or endometrial carcinomas, they are free to grow unchecked without producing symptoms until they have achieved a relatively late stage of growth, and there is no effective screening process or minimally invasive biopsy procedure available to assist in early diagnosis. Most of these tumors are carcinomas of surface epithelial origin, and of these carcinomas, approximately three quarters fall into the category of high grade serous carcinoma (HGSC).

SEROUS CARCINOMA: A SERIOUS CARCINOMA

HGSC is one of the most deadly gynecologic malignancies. The vast majority of patients (90% in some studies) present with stage III or IV disease, with spread beyond the pelvis and regional lymph node metastases common. Although surgical debulking to remove all visible tumor (“cytoreduction”) followed by cytotoxic chemotherapy frequently results in a progression-free interval, the rule for advanced stage disease is eventual recurrence and death from disease.

As HGSC often presents at a relatively advanced stage with widespread peritoneal involvement, it can be difficult to determine the exact site of origin. Traditionally, the site of origin of HGSC has been assigned to the organ most affected, and it was long thought that the majority of these cases arose within the ovary. Primary fallopian tube tumors were classified as such when the tumor was either restricted to the tube, or when the fallopian tube was most affected, with other sites showing only minimal involvement or a different histology entirely. There has been a recent shift in thinking about the putative site of origin of HGSC, resulting from increased scrutiny of the changes occurring within the fallopian tube in women undergoing risk-reducing salpingo-oophorectomy (RRSO).

MOLECULAR FEATURES OF HGSC

The signature molecular alteration associated with HGSC is mutation

In this edition, Dr. Nicholas Byrne discusses our evolving understanding of ovarian carcinoma, its putative tubal origin within serous tubal intraepithelial carcinoma in most cases, and the role of risk reducing salpingo-oophorectomy.
of the TP53 tumor suppressor gene, which is seen in up to 80% of cases. In the practice of pathology, mutations in the TP53 gene correspond to abnormal staining for the gene protein product p53, which can be demonstrated using immunohistochemistry. An abnormal staining pattern is identified when staining is either diffusely positive (due to a missense mutation resulting in accumulation of the abnormal, nonfunctional protein) or completely negative (“null” phenotype). Loss of functional p53 results in decreased apoptosis in the setting of DNA damage and permits the accumulation of additional mutations resulting in high levels of chromosomal instability.

Hereditary Cancer Syndromes

Women with an inherited mutation in either the BRCA1 or BRCA2 gene are predisposed to the development of ovarian and breast carcinoma, with an estimated lifetime risk of ovarian cancer of 57% and 27%, respectively. The majority of these cancers will be HGSC. For this reason, risk-reducing salpingo-oophorectomy (RRSO) is a well-established procedure in these patients for reducing the lifetime risk of HGSC. RRSO is also frequently recommended in women without a detectible mutation in BRCA1 or 2 who have a strong family history of breast or ovarian carcinoma, as there are both deleterious mutations in BRCA1/2 which are not well characterized as well as mutations in related genes that are not detected by current screening regimens.

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HGSC, STIC, and The Role of Tubal Epithelium

It has long been held that epithelial transition zones, such as the squamo-columnar transformation zones in the cervix, anus, and esophagus, are predisposed to the accumulation of genetic injuries which can lead them down the pathway of malignant transformation. Under this paradigm, the tubal-mesothelial junction, where the external surface of the fallopian tube fimbriae showing secretory-type tubal epithelium transitions to the mesothelial-lined surface of the ovary, is another area of potential metaplasia subject to DNA damage.

Careful examination of the tubal fimbriae in cases of HGSC of presumed ovarian origin has demonstrated neoplastic lesions within fallopian tube epithelium which have identical morphology and genetic signatures in up to 60% of cases. These lesions are not detected in other subtypes of ovarian cancer, such as endometrioid or clear cell adenocarcinoma. With the rise of RRSO, early tubal serous carcinoma can be seen in 2-10% of women in the absence of grossly evident HGSC. These lesions have been termed “serous tubal intraepithelial carcinoma” (STIC), and can be diagnosed in the presence of areas of atypia and proliferation in the distal fallopian tube. Foci suspicious for STIC can be evaluated using immunohistochemical stains for p53 and cell cycle markers such as Ki-67/MIB-1 to confirm proliferative activity.

Detection of small, but nonetheless clinically significant, foci of HSCG or STIC depends on adequate microscopic visualization of the tubal fimbriae. To that end, physicians at the Brigham and Women’s
Hospital and Dana Farber Cancer Institute have developed a method of processing fallopian tubes removed for RRSO which maximizes the detection of abnormalities in the distal tube. This method has been dubbed “sectioning and extensively examining the fimbrial end”, or the SEE-FIM protocol.

**CURRENT THINKING**

High grade serous carcinoma can have its origin in the fallopian tubes (majority), ovarian surface, or peritoneum. HGSC in these latter two sites may in fact be arising in foci of endosalpingiosis (benign inclusions of tubal-type epithelium) or Mullerian epithelial rests (the “secondary Mullerian system”). Other forms of ovarian surface epithelial carcinoma (endometrioid adenocarcinoma, clear cell carcinoma, transitional carcinoma) probably arise from epithelial inclusions (endometriosis, Brenner tumor).

**SO, NOW WHAT DO WE DO?**

Cancer free rates for women who are predisposed to the development of ovarian carcinoma who undergo RRSO are nearly 96%. This compares quite favorably to a cancer free rate of 69% for those managed by close surveillance alone. The evidence seems clear in these cases that RRSO followed by careful pathologic examination to detect STIC or occult HGSC is the right choice. Ultimately, the role of RRSO in patients without a defined family history of breast or ovarian cancer or a known genetic mutation is controversial.

Based on the evolving knowledge of STIC and its implication in the development of pelvic HGSC, we in the medical community are seeing an increase in "opportunistic salpingectomy”—that is, salpingectomy in women who are otherwise considered low risk for the development of ovarian carcinoma, but are undergoing surgery for other indications such as uterine prolapse or appendectomy. Alternatively, salpingectomy may be considered as an alternative to simple tubal ligation for sterilization purposes. It will be interesting to note the effect on rates of HGSC in the general population as both clinicians and patients alike increasingly advocate for total salpingectomies as a potential risk-reducing strategy.

Contra Costa Pathology Associates follows established protocols for the submission and microscopic examination of fallopian tube specimens which increase the chances of finding an early, clinically occult HGSC or STIC. When submitting any specimen that includes the fallopian tube(s), it is important to indicate if the procedure is being performed for risk reduction or if the patient has a strong family history of breast and/or ovarian carcinoma. Judicious use of immunohistochemical stains on cases with tubal epithelial abnormalities can assist in detection of occult HGSC or STIC and help identify patients who may need close follow up or additional therapy.

References: