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Editorial

Occult ovarian cancer at the time of risk-reducing salpingo-oophorectomy

Women who carry deleterious mutations of the *BRCA1* or *BRCA2* gene are the largest identifiable population at high risk for ovarian cancer and account for 10% of all cases. The lifetime risk of ovarian cancer in women with *BRCA1* mutations ranges from 20 to 65% and the lifetime risk in *BRCA2* mutation carriers is approximately 20% [1,2]. Women with *BRCA1/2* mutations are also known to be at risk for peritoneal carcinomatosis and fallopian tube cancer in addition to breast and ovarian cancer.

Although current ovarian screening strategies remain inadequate for identifying early cancers, risk-reducing salpingo-oophorectomy (RRSO) has been shown to effectively reduce the risk of ovarian and fallopian tube cancer in women with BRCA mutations (hazard ratio 0.04 (95% CI 0.01–0.16) [3] and 0.15 (95% CI 0.02–1.31) [4]. RRSO also reduces the risk of breast cancer by 56% in *BRCA1* carriers and 46% in *BRCA2* carriers [5,6]. The majority of women who test positive for *BRCA1* and *2* mutations are now choosing to undergo RRSO after childbearing [7].

A number of authors have reported on the occurrence of occult cancers found at the time of RRSO [3–12]. Finch et al. [13] have extended their earlier study and in this issue now report data on one of the largest single institutional series of 159 *BRCA1* and *BRCA2* carriers who underwent RRSO during a 12-year period from 1992 to 2004. From the year 2000 onward, their protocol was modified such that all patients were screened prior to surgery with an endovaginal ultrasound and serum CA125. In addition, the pathologic evaluation of the surgical specimens included serial sectioning of both tubes and ovaries. Peritoneal cytology was performed in 148 cases. The authors report several important findings: (1) There was a higher frequency of occult cancer in *BRCA1* carriers than in *BRCA2* carriers; (2) the number of occult cancers increased with age; (3) there was a high rate of fallopian tube cancer or tubal involvement; (4) almost all cancers were microscopic and early stage and not detected by prior screening; and (5) peritoneal biopsy identified microscopic metastatic cancer in one case.

Overall, 7 (4.4%) occult cancers were detected, and only 2 of these were visible at surgery. Interestingly, 6 of the 94 (6.4%) *BRCA1* carriers had occult cancer, while only 1 of the 65 (1.5%) *BRCA2* carriers was found to have occult cancer. This is consistent with the known higher incidence of ovarian cancer in *BRCA1* carriers than in *BRCA2* carriers.

The age at RRSO may correlate with incidence of occult cancer. In this study, the average age of *BRCA1* patients undergoing surgery was 47.0 years and women with *BRCA1* mutations and ovarian cancer was 48.8 years. The average age of women with *BRCA2* undergoing surgery was 48.8 years, but the only patient with cancer was 53 years old. Women with *BRCA1* mutations develop ovarian cancer at a mean age of 51.2 at diagnosis, whereas *BRCA2* carriers are older with an average age of ovarian cancer of 57.5 years [2]. Thus, on average, the *BRCA1* patients undergoing RRSO surgery in this study are closer to the age at which cancer is found. There were no cases of cancer detected in women under age 40, but three *BRCA1* cancers were found between age 40 and 45. This suggests that women with *BRCA1* mutations should consider RRSO before age 40. Because there was only one case of cancer in a *BRCA2* carrier, it is difficult to recommend guidelines for age of RRSO in this group.

An important finding of Finch and colleagues is that six of the seven occult cancers involved the fallopian tubes. Three of these cases only involved fallopian tubes. Paley et al. [11] first reported two cases of fallopian tube cancer in *BRCA1* carriers. Recently, Olivier et al. [8] compared the incidence of primary peritoneal cancer in *BRCA1/2* carriers who had undergone removal of both tubes and ovaries versus that in carriers who had undergone removal of ovaries only. Of the 90 women who underwent RRSO there were no cases of peritoneal papillary serous carcinoma at mean follow up of 12 months. There were three cases of peritoneal cancer in the 38 patients who underwent only bilateral oophorectomy.

Of the 36 cases of occult cancer found during RRSO reported in the literature, there were 14 cases of primary fallopian tube cancer, a prevalence of 39%. Previously, fallopian tube cancers have been associated with *BRCA2,* but in this study, all of the 4 fallopian tube cancers occurred in *BRCA1* cancers. Finch et al. [13] emphasize the need to serially section (2–3 mm) and examine fallopian tubes as well as ovaries in order to detect small cancers. This rigorous pathologic evaluation has been recommended by others and in the study by Powell et al. [12] resulted in a detection rate of occult cancer of 17%. The study of Finch et

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Table 1
RRSO surgical pathologic protocol

1. Counseling for women who are *BRCA1/2*-positive regarding risk-reducing options
2. Consent for definitive staging surgery if cancer is found
3. Laparoscopy (or laparotomy if indicated) with careful examination of:
   • Upper abdomen including diaphragm, liver, omentum, bowel, paracolic gutters, and appendix
   • Pelvis including, ovaries, tubes, uterus, cul-de-sac, and bladder peritoneal
4. Biopsy of suspicious areas (or random biopsy of omentum/peritoneum)
5. Complete removal of both fallopian tubes and ovaries.
   • Use a retroperitoneal approach dividing ovarian vessels 2 cm proximal to ovary
   • Remove as much of the fallopian tube as possible
   • Remove specimens in an endoscopic sac to avoid intraperitoneal spillage and disruption of the epithelial surfaces
6. Peritoneal cytology
7. Pathologic microsectioning (2–3 mm) and examination of all ovarian and fallopian tube tissue
8. Postoperative multidisciplinary counseling to review pathology and further treatment planning if microscopic cancer is found

al. is consistent with previous studies demonstrating that screening with serum CA125 and endovaginal ultrasound does not appear to detect any of these cancers.

Finally, Finch et al. speculate on the cell of origin of these occult cancers, suggesting that fallopian tube rather than ovary may be a primary site. Although this hypothesis challenges current theory that these cancers develop from inclusion cysts of surface epithelium of the ovary, it remains speculative and will have to await further study. It is noteworthy that most of the cancers detected at RRSO were early stage. As opposed to the cancers found by screening that are often late stage at detection, the early stage of occult cancers at RRSO supports the potential benefit that RRSO may have on survival.

The frequency of occult cancers found at RRSO ranges from 2.3 to17%, the variance being largely accounted for by the rigor with which these cancers are sought at operation. Estimates may also vary according to differences in age of population, ratio of *BRCA1* and *BRCA2* mutations and high-risk family cases, inclusion of borderline ovarian cancers along with invasive ovarian cancer, and the extent of pathologic sampling.

At UCSF, patients who test positive for *BRCA1*/2 undergo counseling with a multidisciplinary team involving geneticists, gynecologic oncologists, and breast oncologists in order to coordinate risk-reducing strategies across specialties. The surgical pathologic protocol (Table 1) is reviewed with patients. It seems prudent for all patients undergoing RRSO to be counseled regarding their risk of occult cancer, and asked to consent to staging surgery at the time of RRSO if a cancer is detected. The high rates of occult cancer in this population argue that the surgery be performed by an expert in ovarian cancer with awareness of subtle changes indicative of micrometastasis. The recommended risk-reducing salpingo-oophorectomy surgical procedure includes (1) a comprehensive and meticulous inspection of the pelvis, upper abdomen, paracolic gutters, and bowels; (2) careful removal of all ovarian and tubal tissue using a retroperitoneal approach, 2-cm margin on ovary, and removal of all adhesions; (3) pelvic washings; (4) peritoneal or omental biopsy; and (5) evaluation of the diaphragm. There have been no reports of a cornual tubal cancer after RRSO if the uterus is not removed. The addition of hysterectomy should be individualized and risks and benefits discussed with each patient. Finch and colleagues emphasize the need for rigorous microsectioning (2–3 mm) of the fallopian tube and ovaries and meticulous pathologic evaluation of the entire specimen. The present study contributes to the growing literature supporting the recommendation that RRSO surgery and pathologic evaluation be performed in a meticulous and comprehensive fashion by experts in ovarian cancer with the support of a multidisciplinary cancer risk team.

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