Ovarian cancer is the most lethal of all gynecologic cancers. The poor prognosis of ovarian cancer is largely attributable to the fact that patients with the disease present late. Although the symptom index for ovarian cancer may help to identify women with the disease, symptoms are not early signs, and most women are diagnosed at an advanced stage.1,2

Once the malignancy is detected, usually when classified at International Federation of Gynecology and Obstetrics stages III to IV, standard treatment consists of a combination of debulking surgery and chemotherapy, and survival rates have shown little improvement.3 Over the last decade, it became clear that ovarian cancer is not a single disease; different histologic subtypes of epithelial ovarian cancer with different molecular pathogeneses and prognoses can be identified.4 This knowledge will guide future research initiatives to improve early detection of and prognosis for epithelial ovarian cancer.5

OVARIAN CANCER SCREENING

Although ovarian cancer screening cannot prevent cancer, it was long hoped that screening might permit detection at an early stage when a cure is possible. Data from general population screening were disappointing; therefore, a large, more sophisticated screening study began in the 1990s in the United Kingdom.6 Postmenopausal women age 45 or older were randomly assigned to a screening or control group. Women randomly assigned to screening were offered three annual screens that included: cancer antigen 125 (CA125) measurements; pelvic ultrasonographies if the CA125 measurement was greater than 30 U/mL; and referrals for gynecologic counseling if the ovarian volume reached 8.8 mL or greater. The development of epithelial ovarian cancer was the study endpoint. The median survival of women with index cancers was longer for the screened group than for the control group (72.9 vs. 41.8 months; p = .01), however, the number of deaths attributable to ovarian cancer did not differ.6 To further improve screening results, a new ovarian cancer risk algorithm was designed using pelvic ultrasonography and trends in serum CA125. This algorithm was developed by the U.K. Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) group, another large screening study.7 Outcomes of the UKCTOCS study showed a favorable stage distribution using the risk of ovarian cancer algorithm, however, there was no notable survival benefit in the screened group compared with the control group.8 In the United States, the Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial investigators randomly assigned women between age 55–74 to an annual screening group and a control group. The screened group underwent an annual pelvic ultrasound and serum CA125 measurement. Increased morbidity was reported owing to high false-positive results (8%) in the screening group, which resulted in women undergoing surgery, however, no reduction in ovarian cancer mortality by screening was found.9

Because the positive and negative predictive value of screening depends on the incidence of the disease, screening was
expected to be more effective for a high-risk population. The U.K. Familial Ovarian Screening Study (UKFOCSS) was developed as a prospective cohort study to assess the value of screening in a high-risk population specifically. The UKFOCSS recruited more than 5,000 high-risk women between 2002 and 2009, and screening was performed with four monthly CA125 measurements analyzed by the risk of ovarian cancer algorithm. Although the final UKFOCSS results are not yet available, screening is not expected to improve ovarian cancer-specific survival nor to be cost-effective.

HEREDITARY OVARIAN CANCER

Since the BRCA genes were discovered in 1994 and 1995, clinicians worldwide have begun developing guidelines for a systematic ovarian cancer screening program for women with BRCA1/2 mutations, consisting mostly of an annual pelvic ultrasound and serum CA125 measurement.12-16

Lynch syndrome (LS) is another hereditary syndrome with an increased ovarian cancer risk. LS is an autosomal dominant predisposition characterized by germline mutations in one of four DNA mismatch repair genes: MLH1, MSH2, MSH6, and PMS2.17 For female carriers with LS, endometrial cancer is, after colon cancer, the most common tumor type with a cumulative lifetime risk of 21%–71%; the risk of ovarian cancer is between 6% and 12%.18 Because of these high cancer risks, women with LS are regularly surveyed. Endometrial cancer surveillance seems to be effective in early detection of endometrial cancer10-21; however, the value of surveillance for ovarian cancer has not yet been proven.19,22

In a recent review on ovarian cancer in LS, the mean age of women with LS and ovarian cancer was 45.3 years and patients had a wide age range of onset (between age 19–82).23 For these patients, ovarian cancer was mostly diagnosed at an early stage (International Federation of Gynecology and Obstetrics stage I–II), exhibited a variety of histopathological subtypes (frequently endometrioid or clear cell), and had a survival rate of 86%.23 Data on the role of surveillance in the detection of ovarian cancer in women with LS were scarce, and the early stage could not be attributed to screening.23

KEY POINTS

- Ovarian cancer screening is not effective in early detection of the disease.
- Most, if not all, high-grade serous ovarian cancers arise in the fallopian tube.
- All women with epithelial ovarian cancer should be offered genetic counseling and testing to reduce morbidity and mortality for patients and their relatives.
- The only effective strategy to prevent high-risk women from dying of the disease is to remove the ovaries and fallopian tubes before the cancer incidence rises.
- Research in the field of hereditary ovarian cancer is an example of a joint effort and fruitful collaboration between researchers on both sides of the Atlantic ocean.

TIME TO STOP OVARIAN CANCER SCREENING

After 2 decades of ovarian cancer screening, and despite major efforts in large prospective trials, no evidence of a survival benefit of screening has been reported. Clinicians, almost simultaneously in the United States and European Union, began to omit gynecologic screening and instead adopted risk-reducing salpingo-oophorectomy (RRSO) and reported on their results.24-30 In 2009, a meta-analysis on risk-reduction estimates showed that RRSO, performed at ages 35–40 for BRCA1 and 40–45 for BRCA2 mutation carriers (i.e., before the cancer incidence rises31), is effective in the detection of more than 96% of BRCA-associated ovarian cancers (hazard ratio, 0.21; 95% CI, 0.12–0.39).32

NEW PARADIGM OF OVARIAN CANCER IN BRCA1/2 MUTATION CARRIERS

Since the adoption of RRSO for BRCA1/2 mutation carriers, increasing percentages of fallopian tube (pre)malignancies have been found. In 1998, Dubeau33 was the first to propose that the various ovarian cancers (serous, endometrioid, mucinous, and clear cell) resemble the epithelium of the fallopian tube, endometrium, endocervix, and gastrointestinal tract, respectively. In 2001, a group of Dutch researchers published a small series on the fallopian tubes of high-risk women and found preneoplastic lesions in benign fallopian tube tissue, not in controls.34 One patient, a BRCA1 mutation carrier, showed loss of the wild-type BRCA1 allele in a severely dysplastic lesion of the distal fallopian tube.34 The publication by Piek et al34 opened the eyes of many pathologists around the world, including Crum and colleagues35 in Boston, Massachusetts, who were the most successful in further elaborating the new paradigm. They were the first to describe the phenomenon of tubal intraepithelial carcinomas, later designated serous tubal intraepithelial carcinomas. From that point, fallopian tubes were more carefully examined, which resulted in an increasing incidence of pre-malignant and early stages of high-grade serous cancer in prophylactically removed fallopian tubes.36-39 Many research projects have since been initiated and are still ongoing to find definitive evidence that the fallopian tube is the tissue of origin of pelvic high-grade serous cancer.40,41

IDENTIFICATION OF MUTATION CARRIERS

Since the isolation of BRCA1/2, the National Comprehensive Cancer Network, which is an alliance of leading U.S. cancer centers, and various family cancer clinics in Europe have developed guidelines for surveillance and prophylactic surgery.12,14,16 More recently, with the introduction of next-generation sequencing and the availability of gene panels, genetic testing for patients with ovarian cancer and family members of mutation carriers is within reach of many women. Year by year, the costs for genetic testing have dropped dramatically, and genetic counseling and testing was recently incorporated in practice guidelines in the United States and Europe.42,43 However, referral for genetic counseling and testing is not implemented among all patients with ovarian cancer in the United States and Europe, and
accessibility differs among patient groups. A recent study on adherence to National Comprehensive Cancer Network guidelines showed differences in genetic testing for patients with ovarian cancer in the United States: women were more frequently tested if they were younger at diagnosis, had a lower stage of ovarian cancer, were white, had private/managed care insurance, and had a family history of cancer. Adherence and access to genetic counseling guidelines in different European countries has not yet been studied. Because genetic counseling and testing of all patients with ovarian cancer can reduce morbidity and mortality from ovarian (and breast) cancer among their relatives, and because prophylactic surgery is cost-effective, referral of all women with epithelial ovarian cancer should be encouraged, regardless of age, histologic type, and family history.

**REFERENCES**


Education Committee statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol.* 2007;107:159-162.


