Genetic Risk and Gynecologic Cancers

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KEYWORDS

• Gynecologic cancer • Genetic • BRCA • Lynch syndrome

Approximately 5% of endometrial cancers and 10% of ovarian cancers can be attributed to an inherited predisposition.[1,2] Given the current incidence of these diseases in the United States, hereditary cancer syndromes will lead to approximately 2200 new cases of ovarian cancer and 2300 new cases of endometrial cancer in 2011.[3] Hereditary breast and ovarian cancer (HBOC) syndrome and Lynch syndrome account for most inherited gynecologic cancers. Other syndromes associated with gynecologic malignancies, such as Cowden syndrome, Li-Fraumeni syndrome, and Peutz-Jeghers syndrome, are rare.

Since the identification of the *BRCA1* and *BRCA2* genes and Lynch syndrome genes almost 20 years ago, significant advances have been made in the management of individuals who carry these gene mutations. In addition, important discoveries related to prognosis and treatment of the patient who has ovarian cancer with a *BRCA1* or *BRCA2* gene mutation have highlighted the role of genetic testing in the care of gynecologic oncology patients. This article reviews the 2 main inherited cancer syndromes relevant to gynecologic cancers, HBOC syndrome and Lynch syndrome.

HBOC SYNDROME

HBOC syndrome is caused by mutations in the *BRCA1* or *BRCA2* genes, which were first identified and cloned in the early 1990s.[4,5] The prevalence of mutations in *BRCA1* and *BRCA2* among the general population has been estimated to be as high as 1 in 400.[6] However, this varies among different populations. In certain populations that have undergone a period of relative isolation, founder mutations in *BRCA1* and *BRCA2* have been identified. For example, Ashkenazi Jews have a prevalence of approximately 1 in 40.[7]

BRCA1 is localized to chromosome 17q, whereas *BRCA2* is localized to chromosome 13q. As tumor suppressor genes, the proteins coded for by *BRCA1* and *BRCA2* are involved in recognition and repair of DNA damage, specifically

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double-stranded DNA breaks.[8] They are large genes, with *BRCA1* having 24 exons and *BRCA2* having 27 exons.[9] More than 1200 inherited mutations have been found to occur throughout each gene.[8,10] Approximately 80% of these mutations are either nonsense or frameshift mutations resulting in truncated, nonfunctioning protein.[8]

Women with a *BRCA1* mutation have a risk of ovarian cancer by age 70 years of 39% to 46% and a lifetime risk of breast cancer by age 70 years of 65% to 85%. Reported risks of ovarian and breast cancers in women by age 70 years among *BRCA2* carriers are 10% to 27% and 45% to 85%, respectively.[9,11] Germline *BRCA1* and *BRCA2* mutations express incomplete penetrance. Furthermore, penetrance can be highly variable within families with the same BRCA mutation.[12]

BRCA mutation carriers are also at risk for several other cancers. Those rarer cancers reported to be associated with BRCA mutations are male breast, pancreatic, and prostate cancers, although lifetime risk of these cancers is low compared with female breast and ovarian cancer. Other malignancies, such as melanoma and biliary cancers, have also been reported to occur in BRCA carriers.[12–16] Aside from malignancies, there are no known physical abnormalities or other conditions associated with BRCA mutations.

Pathology of BRCA-associated Ovarian Cancers

Multiple studies have noted that BRCA-associated ovarian cancers are more likely to be high-grade serous adenocarcinoma than sporadic ovarian cancers. Although only 44% to 59% of sporadic ovarian cancers are serous, up to 86% of BRCA-associated ovarian cancers have serous histology.[12,17,18] In addition, endometrioid, mucinous, and low malignant potential tumors are rarely diagnosed in BRCA-positive women.[19–21] Low-grade serous cancers are also unlikely to be part of the BRCA cancer spectrum.[22] When comparing the histology of *BRCA1* and *BRCA2* patients, no difference has been found.[17,21,23]

Theory of the Fallopian Tube as a Potential Origin of BRCA-associated Serous Cancers

Most pelvic serous carcinomas are classified as ovarian. These cancers have been presumed to arise from the ovarian surface epithelium.[18] However, there has recently been increasing interest in the fallopian tube as the potential site of origin of many BRCA-associated serous malignancies, including cancers that are typically diagnosed as ovarian.

This hypothesis developed as BRCA carriers and other high-risk women began to undergo risk-reducing salpingo-oophorectomy (RRSO) in the 1990s. The pathologic examination of these patients revealed early-stage, asymptomatic malignancies, with many located in the distal tube or fimbria. Most of these tumors were microscopic.[24–31] However, not all of the tumors diagnosed in these studies were found in the tube. According to a recent summary of the published cases of malignancies found in RRSO specimens in BRCA carriers, approximately 21% of occult cancers involved the ovary alone, bringing into question whether the fallopian tube is the sole site of origin for serous carcinomas.[31] Nevertheless, that most of the tumors found on RRSO are tubal is in contrast with the fact that fallopian tube cancer is rarely diagnosed in patients who present with late-stage serous carcinomas, with an incidence rate of only 0.41 per 100,000 women.[32]

To explain why fallopian tube carcinomas are diagnosed more frequently in early occult malignancies than in patients with large tumors or metastatic disease, it has been proposed that many BRCA-associated pelvic serous carcinomas originate in the fallopian tube and subsequently spread to the ovary and other peritoneal surfaces. A lesion called serous tubal intraepithelial carcinoma (STIC) has been hypothesized to