Ovarian Cancer in Hereditary Cancer Susceptibility Syndromes

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KEYWORDS

• Hereditary cancer • BRCA1 • BRCA2 • Lynch syndrome • Ovarian carcinoma • Mismatch repair

Key points

- The ovarian carcinoma histotypes are different diseases, with different associated hereditary risk factors.
- Hereditary breast and ovarian cancer syndrome is associated with increased risk of developing high-grade serous carcinoma, but not other ovarian carcinoma histotypes.
- Lynch syndrome is associated with an increased risk of developing the endometriosis-associated ovarian carcinoma histotypes, clear cell, and endometrioid carcinoma.
- Screening patients presenting with ovarian carcinoma can identify previously undiagnosed hereditary breast and ovarian cancer or Lynch syndrome.

ABSTRACT

Hereditary breast and ovarian cancer (HBOC) syndrome and Lynch syndrome (LS) are associated with increased risk of developing ovarian carcinoma. Patients with HBOC have a lifetime risk of up to 50% of developing high-grade serous carcinoma of tube or ovary; patients with LS have a 10% lifetime risk of developing endometrioid or clear cell carcinoma of the ovary. Testing all patients with tubo-ovarian high-grade serous carcinoma for mutations associated with HBOC syndrome, and all patients presenting with endometrioid or clear cell carcinoma of the ovary for mutations associated with LS can identify patients with undiagnosed underlying hereditary cancer susceptibility syndromes.

OVERVIEW

Hereditary ovarian cancer syndromes have traditionally been underrecognized in medical practice and underreported in the literature. Recently, there has been growing awareness of the hereditary associations with gynecologic malignancies including ovarian cancers. There are 2 common autosomal dominant cancer susceptibility syndromes, hereditary breast and ovarian cancer syndrome (HBOC) and Lynch syndrome (LS), and both may present with ovarian cancers. In the past, the focus has been on breast cancers associated with the former and colorectal carcinomas associated with the latter. We review the epidemiology of these 2 syndromes in relation to ovarian cancers and the importance of accurate ovarian cancer histotype diagnosis in identifying these syndromes. Recommendations regarding the appropriate testing strategies for patients diagnosed with the high-risk ovarian carcinoma histotypes associated with the 2 syndromes, so as to identify index cases of these 2 syndromes and ensure patients and their families are able to receive appropriate screening and preventive treatment, are discussed.

Most cases of ovarian cancer associated with hereditary susceptibility are due to the autosomal dominant hereditary cancer syndromes HBOC

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and LS. The role of pathologists in identifying patients with these syndromes at the time of ovarian cancer diagnosis is reviewed. An awareness of the ovarian carcinoma histotypes that are associated with these 2 cancer syndromes is of critical importance clinically and criteria for accurate diagnosis of ovarian carcinoma histotypes, their associations with HBOC and LS, and the clinical features of these syndromes, are presented in this review.

OVARIAN CARCINOMA

The World Health Organization (WHO) has reclassified ovarian carcinomas (formerly referred to as surface epithelial-stromal carcinomas) into 5 histotypes: high-grade serous carcinoma, low-grade serous carcinoma, clear cell carcinoma, endometrioid carcinoma, and mucinous carcinoma.[1] Each of these carcinomas is distinct in its histogenesis, molecular abnormalities, presentation, and outcome. The ability of pathologists to reproducibly diagnose each histotype has improved remarkably over the past decade,[2,3] with increased understanding of the morphologic features, immunohistochemical profile, and molecular characteristics, and this, in turn, has created opportunities for improved recognition of patients whose ovarian carcinoma is a manifestation of HBOC or LS.

HIGH-GRADE SEROUS CARCINOMA

High-grade serous carcinoma (HGSC) accounts for 225,000 new cancers annually worldwide and 140,000 deaths.[4] HGSC is the most common ovarian carcinoma histotype (68%) and accounts for a disproportionate amount of the morbidity and mortality associated with ovarian cancer. Recently, our understanding of this cancer has undergone very significant modifications. Serous carcinoma was formerly divided into low-grade, intermediate-grade, and high-grade groups (grade 1–3, respectively), but in the revised WHO classification, serous carcinomas are divided into low-grade serous carcinoma and high-grade serous carcinoma.[1,5] It must be emphasized that low-grade and high-grade serous carcinomas are not part of a continuum of disease, with an arbitrary cut point between the low-grade and high-grade cancers and frequent progression from low-grade to high-grade. They are 2 distinct cancers and differ with respect to clinical, morphologic, and molecular characteristics. It is also possible to reproducibly distinguish between them in practice, and this distinction does have clinical implications, including differences in association with hereditary cancer syndromes. HGSC architecturally shows papillary, solid, and gland formation, with these architectural patterns frequently coexisting in a tumor. Indeed, the variability in tumor architecture (intratumoral heterogeneity) is characteristic of this tumor type, and reflects the underlying molecular abnormalities. The tumor cells consistently show high-grade nuclear features, with pleomorphism and a high mitotic rate and frequent abnormal mitotic figures.

Comprehensive profiling of HGSC through The Cancer Genome Atlas project has revealed that *TP53* mutations are ubiquitous, being present in more than 95% of cases.[6] *BRCA1* or *BRCA2* are also mutated or expression is lost through promoter methylation (*BRCA1*) in approximately 40% of cases. Apart from these mutations, however, there are few recurrent mutations in HGSC, which are characterized by chromosomal instability and aneuploidy, which leads to rapid accumulation of a wide range of structural abnormalities throughout the genome. There are frequent defects in DNA repair through homologous recombination. During tumor progression and spread, there is a high degree of intratumoral genetic heterogeneity, such that in samples from 4 different sites, in a single patient, only 50% of genetic abnormalities will be found in all 4 samples.[7] The mutant *TP53* is reflected in abnormal p53 immunostaining in most cases, manifest as either greater than 80% of cells showing intense nuclear staining or complete loss pattern, with no staining of tumor cell nuclei.[8] Any degree of immunostaining for p53 between these extremes of “all or nothing” is wild-type staining pattern and reflects an intact *TP53* gene.

Our understanding regarding site of origin of HGSC has also changed dramatically in recent years.[9] Formerly, based on the dominant mass theory, which assigned primary site based on the largest mass, most HGSCs were considered primary ovarian tumors, albeit with bilateral ovarian involvement in most cases. Very few cases were thought to have arisen from the fallopian tubes based on the formerly used criteria. The presumed histogenesis was of ovarian surface epithelium, which is of mesothelial derivation, undergoing Müllerian metaplastic change to tubal-type epithelium. Neoplastic changes then took place as a result of trauma and inflammation during ovulation.[10,11] One weakness of this theory was the lack of a recognizable precursor lesion. There is now overwhelming evidence that most HGSCs arise from the epithelium of the fallopian tubes and specifically the fimbriated or distal portion.[9] The in situ lesion, and earliest detectable manifestation of HGSC, is serous tubal intraepithelial carcinoma (STIC) (**Fig. 1**). Although apparently in situ,