Imaging and Screening of Hereditary Cancer Syndromes

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KEYWORDS

• Hereditary cancers • Imaging findings • Surveillance

KEY POINTS

- There is a wide spectrum of hereditary cancer syndromes that predispose patients to the early onset of phenotypically distinct tumors in specific organ systems.
- Clinical management of patients with these syndromes is challenging because of a complex interplay of factors, including aggressive tumor histobiology, tumor location, bilateral tumors, advanced disease at presentation, and multiorgan involvement.
- A better understanding of these hereditary syndromes has led to an improved knowledge of underlying tumor genetics and oncological pathways, thus paving the way for molecular diagnostics and targeted therapeutics even in patients with sporadic tumors.
- Laboratory and imaging-based screening strategies allow early diagnosis in asymptomatic patients with a familial predisposition to cancers so as to permit optimal management.

INTRODUCTION

Hereditary cancer syndromes constitute a diverse group of genetic syndromes characterized by the early-onset development of histogenetically distinct neoplasms in specific organ systems in multiple family members.[1,2] These syndromes comprise 3% to 10% of all malignancies in various organ systems.[1] A constellation of clinical syndromes and imaging phenotypes allow characterization of select hereditary cancer syndromes. The finding of specific bilateral tumors and multiorgan involvement may suggest a diagnosis of a hereditary tumor syndrome. A radiologist may be the first physician to alert the clinician to a specific diagnosis of a genetic syndrome based on pathognomonic imaging findings, such as bilateral, multiple renal angiomyolipomas in a patient with tuberous sclerosis.[1,3] This finding may trigger further genetic tests to establish the diagnosis as well as to screen other family members.

Tumors in patients with hereditary syndromes present significant challenges to patient management because of a complex interplay of various factors, including aggressive tumor biology, tumor location, bilateral tumors, advanced disease, and multiorgan involvement.[2] Increased impetus for a better understanding of tumor genetics and pathways in select hereditary syndromes has led to smarter screening strategies as well as the development of novel molecular diagnostics and therapeutics. Evolving paradigms of prophylactic risk-reducing bilateral salpingo-oophorectomy or, more recently, bilateral salpingectomy in patients with BRCA syndromes provide an excellent example of how

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recent advances in pathology and genetics have affected patient management.[4] Detailed studies of these uncommon syndromes have also led to better understanding of histogenesis and the biological diversity of sporadic cancers. The incorporation of poly-ADP-ribose polymerase (PARP) inhibitors in chemotherapy regimens to treat patients with sporadic, ovarian, high-grade serous carcinomas based on the BRCA component of these tumors is a case in point.[5] A plethora of drugs currently available to treat patients with advanced clear cell renal cell carcinomas (RCCs) can be traced to the elucidation of the role of the *VHL* gene in tumorigenesis and the knowledge of impaired VHL–mammalian target of rapamycin (mTOR) pathways in sporadic, metastatic kidney cancers.[6]

A variety of advanced laboratory tests, including genetic tests, are available to establish the diagnosis of hereditary cancer syndromes. Cross-sectional imaging techniques play an integral role in the screening, early diagnosis, surveillance, and management of patients with these syndromes in conjunction with clinical and pathologic findings.[3,7] Unenhanced whole-body magnetic resonance (MR) imaging has recently been shown to be a safe and excellent cancer-screening tool in children with select hereditary cancer predisposition syndromes given its high sensitivity, specific, and negative predictive values as well as the lack of ionizing radiation.[7–10] The screening and surveillance algorithms in select tumor syndromes designed for early diagnosis in asymptomatic patients are also presented in this article (**Table 1**).

HEREDITARY BREAST AND OVARIAN CANCER SYNDROME

Hereditary breast and ovarian cancer syndrome (HBOC) is an autosomal dominant disorder, associated with increased risk of breast and ovarian cancers.[1,11] The risk of primary peritoneal serous carcinoma; primary fallopian tube carcinoma; and pancreatic, prostate, and colon cancers is also increased.[12] Germline mutations in the tumor suppressor genes, *BRCA1* (chromosome 17q21) and *BRCA2* (chromosome 13q13), which help in maintaining genomic stability through DNA repair, are responsible for the development of HBOC.[1,12] There is a 65% to 75% lifetime risk of breast cancer and 40% to 50% (*BRCA1*) or 10% to 20% (*BRCA2*) risk of ovarian cancer in women with HBOC.[13,14]

Invasive ductal carcinomas are the most common type of breast cancers in HBOC, with significantly higher incidence of triple-negative cancers (estrogen, progesterone, and human epidermal growth factor-2 receptors negative) in *BRCA1* carriers (70% vs 10%–20% of the general population).[15] A well-circumscribed breast mass with sharp margins that mimics a benign lesion is the most common imaging appearance of a BRCA-associated breast cancer on mammogram and ultrasonography (US); malignant calcifications are less frequent on mammography (**Fig. 1**).[16] Given the benign imaging appearance of cancers, all mammographically detected lesions regardless of imaging features should be biopsied in HBOC. Contrast-enhanced MR can detect early-stage and potentially curable breast cancers in this population.[17]

High-grade serous carcinoma is the most common ovarian malignancy in HBOC and typically manifests at an earlier age compared with sporadic cases; most of these tumors originate from the fimbriated ends of the fallopian tubes (**Fig. 2**).[4] Although imaging findings of BRCA-associated ovarian serous cancers are similar to sporadic cases, tumors tend to be exquisitely sensitive to PARP inhibitors and platinum agents.[18,19] Primary peritoneal serous carcinoma and primary fallopian tube carcinoma are uncommon malignancies that can develop in HBOC, and show many similarities with serous ovarian cancer; currently, all 3 cancers are grouped as extrauterine pelvic serous carcinomas and are managed in a similar fashion.[18]

HBOC should be suspected in individuals with either a personal or family history of breast cancer diagnosed before the age of 50 years, triple-negative breast cancer, and extrauterine pelvic serous carcinomas.[1] Genetic counseling, followed by appropriate genetic testing, has to be performed in these individuals and their family members. The National Comprehensive Cancer Network (NCCN) recommends breast MR imaging and/or mammogram starting between the ages of 25 and 29 years and discussion of prophylactic mastectomy in HBOC.[20] Screening with a transvaginal sonogram and CA (cancer antigen)-125 levels has not been useful in reducing mortality from ovarian cancer; the NCCN recommends risk-reducing bilateral salpingo-oophorectomy between the ages of 35 and 40 years.[21]

LYNCH SYNDROME

Also known as hereditary nonpolyposis colorectal cancer (CRC), Lynch syndrome (LS) is an autosomal dominant condition that accounts for approximately 3% of CRCs and 2% to 3% of all endometrial cancers.[22] In patients with LS, there is also increased the risk of cancers of