# Prophylactic Gynecologic Specimens from Hereditary Cancer Carriers

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**KEYWORDS**

• Risk-reducing salpingectomy • Salpingo-oophorectomy • BRCA • Lynch syndrome
• Prophylactic surgery • Hereditary cancer • Endometrial cancer • Ovarian cancer

**Key points**

- Risk-reducing surgery, including salpingo-oophorectomy and hysterectomy, is becoming increasingly common as more women are identified as being at genetic risk for endometrial and/or tubal/ovarian cancer.
- The distal end of the fallopian tube and the fimbria from all salpingectomy specimens should be processed to maximize histologic assessment of tubal epithelium.
- The recognition and classification of high-grade serous carcinoma precursor lesions in the tube are more accurate with the addition of immunohistochemistry.

## ABSTRACT

Hereditary breast ovarian cancer and Lynch/hereditary nonpolyposis colorectal cancer syndrome account for most hereditary gynecologic cancers. In the absence of effective cancer screening and other preventative strategies, risk-reducing surgery in women who are known to be at genetic risk of BRCA-associated or of Lynch syndrome carcinomas is effective in significantly decreasing the lifetime risk of developing malignancy. Reflex genomic testing of high-grade ovarian cancers and reflex immunohistochemistry in endometrial cancers will lead to greater recognition of germline-associated cancers. Approaches to processing surgical specimens, the recognition and classification of cancer precursor lesions, and differentiation from their mimics are discussed.

## OVERVIEW

Hereditary gynecologic cancers are largely accounted for by 2 syndromes: hereditary breast ovarian cancer (HBOC), and Lynch/hereditary nonpolyposis colorectal cancer syndrome. As with other hereditary syndromes, it is now apparent that the traditional clinical features of multiple affected family members, multiple types of cancers, and early age of onset underestimate the incidence of cancers associated with inherited mutations. A recent study indicated that 24% of unselected ovarian cancers were associated with germline mutations, and that more than 30% of these mutation carriers had no known family history.[1]

Mutations of *BRCA1* and *BRCA2* account for most ovarian, tubal, and peritoneal cancers in HBOC. Inherited mutations of the BRCA genes

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increase the lifetime risk of developing ovarian/tubal/peritoneal carcinoma from 1.39% in the general population to 40% to 60% (*BRCA1*) and 11% to 27% (*BRCA2*) in mutation carriers. High-grade serous carcinoma (HGSC) is the histotype most consistently associated with BRCA1 and BRCA2 mutations, and as many as 25% of women with a diagnosis of HGSC carry a germline mutation.[1–3] Other rare germline mutations have been reported in HGSC with some familial risk, most of which encode proteins that have roles in BRCA1/BRCA2 DNA repair pathways, including *BARD1*, *BRIP1, RAD50*, *RAD51C*, *RAD51D*, and *PALB2*.[1,4] A significant percentage of familial ovarian cancers are not associated with known deleterious mutations, and it is likely that other less common and less penetrant genetic risk factors have not yet been discovered.

Screening for HGSC has been shown to be ineffective in reducing mortality, and although the use of oral contraception has been demonstrated to reduce risk in both sporadic and BRCA-associated ovarian cancers, risk-reducing salpingo-oophorectomy (RRSO) is the most effective preventative method. Risk-reducing surgery decreases the risk of HGSC by 90%, but also reduces cancer-related mortality and overall mortality.[5] The term "risk-reducing salpingo-oophorectomy" is favored over prophylactic oophorectomy, reflecting (i) the inclusion of fallopian tube carcinoma in the BRCA-mutation associated cancer phenotype and (ii) the fact that a small percentage of women undergoing preventative surgery continues to have a small risk of developing carcinoma despite removal of the ovaries and fallopian tubes.[6] Carcinomas of the uterus do not appear to be associated with this syndrome, and therefore, prophylactic hysterectomy is not routinely performed in these women.

Current guidelines from the National Comprehensive Cancer Network and the Society of Gynecologic Oncologists advise that RRSO take place between the ages 35 and 40. However, most women known to be at risk do not undergo surgical intervention before the recommended age, in part due to variations in assessment of risk, availability of genetic counseling and testing, and concerns related to early surgical menopause. In addition, only a small percentage of carriers are identified, and despite current recommendations to refer women with epithelial ovarian cancer for genetic counseling and elective genetic testing,[7] only a minority of women with a new diagnosis of high-grade serous carcinoma is tested in most jurisdictions, and therefore, many women at genetic risk are not currently identified.

Lynch syndrome (LS), the most common hereditary cancer syndrome, is an autosomal-dominant disorder associated with germline mutations in DNA mismatch repair genes. The most frequently affected genes are *hMLH1*, *hMSH2*, *hMSH6*, and, less commonly, *hPMS2*, and mutations in these genes usually lead to microsatellite instability. Microsatellite instability is frequent in endometrial cancer, about 20% to 25%, but in most cases, this is due to *hMLH1* promoter hypermethylation and is not reflective of an inherited disorder.

Women with LS have a 60% lifetime risk of endometrial carcinoma, and a 12% risk of ovarian cancer, and in women, the diagnosis of the gynecologic cancer may be the sentinel event indicating the association with LS.[8] Although affected women are at increased lifetime risk for ovarian cancer, the proportion of ovarian cancers associated with LS is relatively low.[1]

Reflex screening of appropriate cancer samples (namely colon and endometrial cancers) with mismatch repair immunohistochemistry to triage patients for LS testing is rapidly becoming standard of care.[9–11] Furthermore, subtype-specific reflex testing strategies have been proposed for ovarian cancer, with some centers performing reflex testing on endometrioid, clear cell, and undifferentiated ovarian carcinomas.[12] LS has implications for both the patient and family members. Because a gynecologic cancer will be the sentinel malignancy in about 60% of women with LS, identification will allow enrollment of these patients in high-risk colon cancer screening programs, which are highly effective.[8] Mismatch repair deficiency, whether of sporadic or hereditary cause, can also inform therapeutic options, such as the use of immune checkpoint inhibitors.[13] Cascade testing of family members to identify unaffected carriers is also critical to facilitate cancer screening and prophylactic surgery in relatives.[14] An added imperative is the potential cost savings for the health care system. As such, with the advent of reflex testing and the drive to identify unaffected family members, prophylactic gynecologic specimens from LS carriers are likely to become more common.

There are other less common and less well-known syndromes associated with gynecologic tumor risk. Cowden syndrome, associated with germline mutations of *PTEN*, increases the lifetime risk of endometrial carcinoma to19% to 28% by age 70.[15] Mutations in *STK11/LKB1* are associated with Peutz-Jeghers syndrome, with an increased risk of adenoma malignum of the cervix and of sex cord stromal tumors of the ovary. Li-Fraumeni syndrome, with germline mutations of