Current and future role of genetic screening in gynecologic malignancies

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The world of hereditary cancers has seen exponential growth in recent years. While hereditary breast and ovarian cancer and Lynch syndrome account for the majority of mutations encountered by gynecologists, newly identified deleterious genetic mutations continue to be unearthed with their associated risks of malignancies. However, these advances in genetic cancer predispositions then force practitioners and their patients to confront the uncertainties of these less commonly identified mutations and the fact that there is limited evidence to guide them in expected cancer risk and appropriate risk-reduction strategies. Given the speed of information, it is imperative to involve cancer genetics experts when counseling these patients. In addition, coordination of screening and care in conjunction with specialty high-risk clinics, if available, allows for patients to have centralized management for multiple cancer risks under the guidance of physicians with experience counseling these patients. The objective of this review is to present the current literature regarding genetic mutations associated with gynecologic malignancies as well to propose screening and risk-reduction options for these high-risk patients.

Key words: BRCA, cervical cancer, endometrial cancer, hereditary cancer, high risk, Lynch syndrome, ovarian cancer, risk reduction, screening

Introduction

The world of hereditary cancers has seen exponential growth in recent years with the identification of new genes associated with gynecologic malignancies as well as a better understanding of the spectrum of potential cancers associated with previously described mutations. The advent of next-generation sequencing, development of hereditary cancer panels, and decreased costs of testing helped to rapidly move the field forward. However, these advances have the potential to provide patients and practitioners with results that have limited evidence to guide them in expected cancer risk and appropriate risk-reduction strategies. The objective of this review is to present the current literature regarding genetic mutations associated with gynecologic malignancies as well as to examine screening and risk-reduction options for these high-risk patients.

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Spectrum of mutations

Ovarian cancer

Ovarian cancer remains the leading cause of death among gynecologic malignancies and up to 24% of the 22,280 new cases diagnosed each year are due to an underlying inherited predisposition.[1,2] While mutations in *BRCA1* or *BRCA2* account for the majority of hereditary ovarian cancers, Lynch syndrome and other genes in the DNA double-strand repair pathway are responsible for a significant proportion of hereditary ovarian cancers.[3-6] Although all of these genes carry a significantly increased lifetime risk of developing ovarian cancer, their risks are not equivalent. Clinicians must take the gene, the personal history, and the family history into consideration when designing a personalized screening and risk-reduction strategy for each individual patient.[7-9]

Mutations in *BRCA1* and *BRCA2* make up 75% of all hereditary ovarian cancers and are inherited in an autosomal dominant manner.[1] Women with *BRCA1* or *BRCA2* mutations are at most increased risk of developing breast and/or ovarian cancers but these two genes also carry an increased risk for other cancers including pancreatic cancer, melanoma, and possibly uterine cancer.[10-12] Women who carry a *BRCA1* mutation have a lifetime risk for developing ovarian cancer of 39-46%, while women who carry a *BRCA2* mutation have a lower lifetime risk of 11-27%.[13-15] In addition, women with *BRCA2* mutations tend to present with both ovarian and breast cancer about a decade later compared to *BRCA1* mutation carriers.[15] In October 2014, the Society of Gynecologic Oncology (SGO) released a clinical practice statement recommending that all women with newly diagnosed epithelial ovarian, tubal, and peritoneal cancers be offered genetic testing for germline *BRCA1* and *BRCA2* mutations.[16] This recommendation has also been endorsed by the National Comprehensive Cancer Network (NCCN).[17]

Lynch syndrome is inherited in an autosomal dominant manner and caused by a mutation in 1 of the 4 mismatch repair genes (MMR; *MLH1*, *MSH2*, *MSH6*, and *PMS2*) or the epithelial cell ashesion molecule (*EPCAM*), which is a regulator of *MSH2*, and Lynch accounts for up to 15% of all hereditary ovarian cancers (Table 1). Lynch-associated ovarian cancers tend to be either endometrioid or clear cell histology[18,19] and individuals with Lynch syndrome are also at increased risk of developing colorectal cancer, endometrial cancer, gastric cancer, small bowel cancer, transitional cell carcinoma of the genitourinary tract, pancreatic cancer, sebaceous

TABLE 1
Outline of current hereditary gynecologic malignancies with surveillance and risk-reduction strategies

Genetic syndrome	Gene	Gynecologic cancer	Cancer risk, %	Surveillance strategy (age to start)[7,17,31,32,37]	Risk-reduction strategy (age to consider)[7,17,a]
HBOC	*BRCA1*	Ovary	39–46	Consider Q6 mo/annual TVUS and serum CA-125	RRSO (35–40 y)
HBOC	*BRCA2*	Ovary	10–27	Consider Q6 mo/annual TVUS and serum CA-125	RRSO (40–45 y)
Lynch	*MLH1*	Ovary Uterus	4–24 25–60	Consider annual TVUS and/or office endometrial sampling	RRSO when childbearing complete (35–40 y) Risk-reducing hysterectomy when childbearing complete
Lynch	*MSH2/EPCAM*	Ovary Uterus	4–24 25–60	Consider annual TVUS and/or office endometrial sampling	RRSO when childbearing complete (35–40 y) Risk-reducing hysterectomy when childbearing complete
Lynch	*MSH6*	Ovary Uterus	1–11 16–26	Consider annual TVUS and/or office endometrial sampling	RRSO when childbearing complete (35–40 y) Risk-reducing hysterectomy when childbearing complete
Lynch	*PMS2*	Ovary Uterus	6[b] 15	Consider annual TVUS and/or office endometrial sampling	RRSO when childbearing complete (35–40 y) Risk-reducing hysterectomy when childbearing complete
HOC	*BRIP1*	Ovary	10–15	No current recommendations	Consider RRSO (45–50 y)
HOC	*RAD51C*	Ovary	10–15	No current recommendations	Consider RRSO (45–50 y)
HOC	*RAD51D*	Ovary	10–15	No current recommendations	Consider RRSO (45–50 y)
Peutz-Jeghers	*STK11*	Ovary (SCTAT) Uterus Cervix (adenoma malignum)	18–21 9 10	Annual pelvic exam and Pap smear (18–20 y) Consider annual TVUS	No current recommendations
Cowden	*PTEN*	Uterus	19–28	Consider annual TVUS and office endometrial sampling (30–35 y)	Discuss hysterectomy upon completion of childbearing
Li-Fraumeni	*TP53*	Ovary[1] Uterus[83]	Elevated[c] Elevated[c]	No current recommendations	No current recommendations
PPAP	*POLD1*	Uterus	Elevated[c]	No current recommendations	No current recommendations

HBOC, hereditary breast and ovarian cancer syndrome; *HOC*, hereditary ovarian cancer; *PPAP*, polymerase proofreading-associated polyposis; *Q*, every; *RRSO*, risk-reducing salpingo-oophorectomy; *SCTAT*, sex cord stromal tumor with annular tubules; *TVUS*, transvaginal ultrasound.

[a] Age may be adjusted based on age of first diagnosis in family; [b] Combined risk of renal pelvis, stomach, ovary, small bowel, ureter, and brain; [c] Mutations carry increased risk, but specific range unknown.

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adenomas, and glioblastoma multiforme (Table 2).[7,20]

Mutations in other genes within the DNA double-strand repair pathway also confer an increased risk of developing ovarian cancer. In particular, mutations in *RAD51C*, *RAD51D*, and *BRIP1* have been shown to have an increased risk of ovarian cancer as high as 10% (Table 1).[3,4,5] Other genes in the DNA double-strand repair pathway, including *PALB2* and *BARD1*, have been investigated for an increased risk of ovarian cancer but none have reached the point of firm recommendations for changing ovarian cancer risk management to date. Mutations in genes within the DNA double-strand repair pathway are inherited in an autosomal dominant manner; however, many of these genes are also associated with Fanconi anemia, which occurs when an individual is homozygous for mutations.

Rare syndromes such as Peutz-Jeghers syndrome (PJS) (*STK-11* mutation), *DICER1* syndrome (*DICER1* mutation), and Li-Fraumeni syndrome (LFS) (*TP53* mutation) also carry increased risks of developing ovarian cancers. PJS carries an increased risk of developing a particular stromal tumor called sex cord tumors with annular tubules of the ovary, *DICER1* syndrome carries an increased risk of developing Sertoli-Leydig ovarian tumors, and LFS carries an increased risk for many cancers that can include ovarian.[1,21-25] Up to 50% of women with Sertoli-Leydig ovarian tumors will have a germline *DICER1* mutation and genetic testing should be considered in all women who present with these tumors.[26] All of these syndromes are inherited in an autosomal dominant manner but can also be caused by de novo mutations. Given the