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The genetic prediction of risk for gynecologic cancers☆

Leslie M. Randall [a,*], Bhavana Pothuri [b]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of California, Irvine, 101 The City Dr. South, Bldg 56, Room 262, Orange, CA 92868
[b] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, NYU Langone Medical Center, 240 E. 38th St., 19th floor, New York, NY 10016

HIGHLIGHTS

- Hereditary cancer syndromes are an important precision medicine opportunity.
- Homologous recombination mutations including BRCA contribute to ovarian cancer.
- DNA mismatch repair defects increase risk for both ovarian and uterine cancers.
- Risks can be significantly reduced with prophylactic surgery or surveillance.
- These mutations can predict response to novel molecular therapies.

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ABSTRACT

Salient to the intent of personalized medicine, hereditary cancer syndromes present significant opportunities in the treatment and prevention of some gynecologic cancers. Mutations in *BRCA1*, *BRCA2*, and DNA mismatch repair genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2* are important causal agents in hereditary breast and ovarian cancer (HBOC) and Lynch syndromes. Though they only account for an estimated 10-18% of ovarian, tubal, peritoneal, and endometrial cancer cases, inherited cancers are imminently preventable if mutation carriers are identified in a timely manner. Population level screening is currently impractical due to low prevalence of disease, cost of testing, and ethical issues associated with testing, so diagnosis of these mutations is limited. Being affected by one of the heritable gynecologic malignancies is a logical entry point into the genetic counseling and testing pipeline for the patient and her family members. Thus, gynecologic cancer providers are uniquely positioned to diagnose germline mutations that can inform prognosis and treatment for their patients in addition to enabling prevention for patients' cancer-unaffected blood relatives, or "previvors". The purpose of this review is to describe our current perspective on testing for and implications of heritable cancer syndromes in the women with ovarian, tubal, peritoneal, and endometrial cancers.

1. Introduction

The diagnosis of hereditary cancer syndromes has, until recently, been reserved for women with ovarian or endometrial cancer who have extensive family history or early onset of disease suggestive of a causal mutation. A technologic explosion coupled with increasingly acceptable options for prevention and targeted chemotherapy are rapidly moving the hereditary cancer topic to the forefront of clinical practice. Genetic counseling and testing has been challenging due to significant risks of testing, in addition to increased resource utilization for quality genetics care. The benefits of testing for hereditary gynecologic cancers include more personalized prognosis-which is improved in BRCA mutation carriers compared to non-carriers, enhanced risk assessment for potentially synchronous cancers, and improved triage to targeted therapies like PARP inhibitors for BRCA carriers [1] and potentially immunotherapy for Lynch carriers [2]. The risks of testing are subject to clinician assumptions and include increased anxiety or depression from positive results, uncertainty over inconclusive results, financial costs of testing, and difficulty navigating the complex landscape of available testing modalities. Identification of women with inherited cancers has, however, not only opened doors for prevention, but has also unexpectedly contributed to our knowledge of the biology of these tumors.

2. Ovarian, tubal, and peritoneal cancers

Once thought to be different diseases, these three malignancies are more alike than not, especially when considering only tumors that result in the peritoneal carcinomatosis phenotype most often associated

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* Corresponding author.
E-mail addresses: lrandall@uci.edu (L.M. Randall), Bhavana.Pothuri@nyu.edu (B. Pothuri).

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with high grade serous or undifferentiated histologies. For the purpose of this review, ovarian, tubal, and peritoneal cancers will be collectively referred to as "ovarian cancers".

2.1. Hereditary breast and ovarian cancer (HBOC)

Families with pedigrees rich in breast and ovarian cancer cases have been the focus of intense research efforts for several decades. From these families, mutations in *BRCA1* and *BRCA2* have proven to be the most common cause of hereditary breast and ovarian cancers, increasing the relative risk for ovarian cancer to 40 times that of the general population [3]. *BRCA* genes encode proteins by the same name that contribute to the repair of double-stranded DNA breaks by homologous recombination (HR), a process in which the damaged DNA is replaced with the proper base pairs using the sister chromatid as a template [4]. Other protein co-factors in the HR process including *RAD51C*, *RAD51D*, *BRIP1*, *PALB2*, *BARD1*, and the MMR genes have been implicated as potential etiologic agents in hereditary ovarian cancer [5]. Their genes are collectively referred to as HR deficiency (HRD) genes, and are also important when mutated in tumors themselves as somatic mutations. Moreover, somatic HRD was a key abnormality identified by the Cancer Genome Atlas analysis of high grade serous ovarian cancers [6].

2.2. BRCA1 and BRCA2

Now 25 years since *BRCA1* was localized to chromosome 17q21 [7], and 21 years since *BRCA2* was mapped to chromosome 13q12.3 [8], the discovery of these tumor suppressor genes has proven to be one of the most impactful in the history of gynecologic cancer. Germline mutations in *BRCA1* and *BRCA2* were identified by linkage analysis in families with clustering of breast cancer cases, with some visibility on associated ovarian cancer [3]. *BRCA* mutations can occur in women or men of any heritage, but specific high-frequency mutations, or founder mutations, occur mainly in Ashkenazi Jewish heritage (*BRCA1* 185delAG, *BRCA1* 5382insC, and *BRCA2* 6174delT) [9], but have also been identified in other races and ethnicities [10–14].

Our current estimation of breast and ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers is derived from higher-risk, referral populations [10,15]. These studies demonstrate both reduced penetrance, meaning not all carriers will develop breast or ovarian cancer, and variable expressivity, meaning the cancer(s) that manifest among carriers can vary. In general, *BRCA1*-associated breast and ovarian cancer cases have a higher incidence than *BRCA2*, and breast cancer is more common than ovarian cancer, which in part is due to sporadic breast cancers in mutation carriers (Table 1). Due to variable expressivity, it is not possible to predict when an individual carrier will manifest ovarian cancer, therefore both *BRCA1* and *BRCA2* carriers are counseled the same with regard to age at which to pursue prevention options. As more diverse populations are tested, like ovarian cancer patients with no family history, our knowledge of penetrance and incidence is likely to expand.

2.3. Testing for BRCA1 and BRCA 2

Since at least 2014, multiple professional societies including the American College of Medical Genetics and Genomics (ACMG) [16], the American Society of Clinical Oncology (ASCO) [17], the National Cancer Comprehensive Network (NCCN) [18], the National Society of Genetic Counselors (NSGC) [16], and the Society of Gynecologic Oncology (SGO) [19] recommend genetic testing for all women with non-mucinous epithelial ovarian, tubal, and peritoneal cancers. Guidance regarding which test to perform, however, is not specific. The extent of testing ranges from screening founder populations for known founder mutations to sequencing *BRCA1* and *BRCA2*, and to performing panel testing of *RAD51C*, *RAD51D*, *BRIP1*, *PALB2*, *BARD1*, and the MMR genes, which explain another 4% of hereditary cancers [5]. Other strategies include starting with low complexity and "reflex" to more complicated testing if initial testing does not diagnose a mutation. In general, the more genes tested, the more non-specific the results with increasing likelihood of encountering a "variant of uncertain significance", or a polymorphism that has not yet been classified as deleterious or benign. Most insurance carriers re-imburse for at least *BRCA1* and *BRCA2* testing, which typically runs $1000-3000 USD, but some might cover more complex panels with higher costs. Multiple vendors now offer *BRCA1* and *BRCA2* and panel testing, and in most cases, which test to order is the prerogative of the clinician, but at times, the third-party payor.

Genetic counselors are an excellent resource to determine which patients need which type of testing while providing invaluable counseling regarding the possibilities of false negative results and testing of family members or "cascade" testing. The availability of trained genetics professionals can vary, so efforts such as telemedicine genetic counseling are underway to improve access [20]. However, when trained genetic counselors are not accessible, it is better for the oncologist to provide counseling and testing than for the cancer-affected patient not to have testing at all. The content of counseling is not currently well-defined, but efforts are underway within the SGO to facilitate this education.

When deleterious mutations are identified, blood-relatives of the affected patient are eligible for genetic testing limited to the identified mutation. A negative result effectively classifies those at general population risk, and family members with positive results are triaged to risk-reducing strategies. There are no specific recommendations for when (at what age) to perform cascade testing. In general testing is not recommended for minors, but it should occur no later than 35 at which time risk-reducing surgery for ovarian cancer is recommended. Many might benefit from earlier testing, particularly when there is a family history of affected individuals under the age of 35.

2.4. Risk-reduction options

The most important aspect of hereditary cancer risk is that it can be significantly modified by prophylactic measures. For women with *BRCA1* and *BRCA2* mutations, the three options to mitigate risk are surveillance, chemoprevention, and risk-reducing surgery. Similar to average risk screening [21], high-risk surveillance of *BRCA* carriers with annual CA-125 and ultrasound has low impact on early detection, and carries the potential harms of unnecessary surgery [22]. A proposed improvement, the risk of ovarian cancer algorithm (ROCA), measures serial CA-125 values longitudinally to detect a velocity increase greater than that of established controls [23], prompting an imaging evaluation. A large prospective, randomized trial of annual ROCA in average risk women, escalated to every 6-12 weeks for abnormal results, reported a sensitivity and specificity of 85.8% (95% confidence interval 95% CI, 79% to 91%) and 99.8% (95% CI, 99.8% to 99.8%), respectively, at the expense of 5 surgeries per invasive cancer. However, only 42% of screen-detected cancers were Stage I or II and these included borderline tumors and other low risk histologies. [24] More research is needed to evaluate frequent, every 3-6 month, ROCA as a strategy for *BRCA* carriers. GOG 199 is one such trial that is currently maturing [25] which to date has reported only a multivariate association between abnormal ROCA and diagnosis of occult cancer at risk-reducing surgery ($p<0.01$) [26].

Chemoprevention is best achieved with combined oral contraceptives (COCs) in women without contraindications to this therapy. Meta-analysis of three case-control studies showed a significant risk reduction of ovarian cancer in *BRCA* mutation carriers with any past COC use (odds ratio [OR]: 0.57; 95% CI: 0.47-0.70) and significant trend by duration of COC use (OR: 0.95; 95% CI: 0.93-0.97; $p < 0.001$) [27].

Table 1
Cumulative incidence of breast and ovarian cancer in mutation carriers by age 70 [3,7]

	BRCA1	BRCA2
Breast cancer	55-78%	45-47%
Ovarian cancer	40%	11-17%