Gynecologic Oncology 152 (2019) 3–6

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

State of the Science

Challenges in the identification of inherited risk of ovarian cancer: where should we go from here?

1. A brief history of genetic testing for ovarian cancer risk

The idea that a mutation in a single gene could lead to a high risk of breast or ovarian cancer used to be a radical idea. It was not until 1990 that Dr. Mary Claire King and her team localized a gene for hereditary breast cancer to chromosome 17q21 [1], which she named *BRCA1*. This discovery set off a race involving multiple research labs around the globe to clone and sequence the gene, ultimately ending in 1994 when a team led by Mark Skolnick became the first to do so [2,3]. Skolnick went on to found Myriad genetics, which then acquired a patent for the sequence of *BRCA1*, followed shortly the next year with a patent for *BRCA2*. Due to the patents, from 1996 to 2013, one company provided all commercial sequencing in the United States for *BRCA1* and *BRCA2*, using PCR amplification and Sanger sequencing. Sanger sequencing will detect small insertions, deletions, and single base pair changes, but not larger genomic rearrangements, which represent around 10% of *BRCA1* and *BRCA2* mutations [4]. Genomic rearrangement testing in the United States became available commercially in 2006 as a separate test, and was made part of the *BRCA1* and *BRCA2* sequencing test in 2013. Next generation sequencing technology was developed in the late 2000's, allowing for massively parallel sequencing of multiple genes at once with substantially lower costs [5], but due to gene patents, panels that included *BRCA1* or *BRCA2* could not be offered, which limited the clinical use of such testing.

The landscape of genetic testing changed dramatically in June of 2013, when the United States Supreme Court ruled unanimously that genes are products of nature and cannot be patented [6], effectively dismissing the patents on *BRCA1* and *BRCA2* and other human genes. Immediately following this decision, multiple companies began offering cancer gene panel tests, and multiplex testing rapidly became standard practice. The main advantage of multiplex testing is the ability to detect mutations in many genes using a single test, increasing efficiency and decreasing costs. The primary downside is that as more genes are sequenced, the likelihood of identifying uncertain results also increases, either in the form of variants of uncertain significance (VUS), or damaging mutations in genes with uncertain contributions to cancer risk.

2. How do genes other than *BRCA1* and *BRCA2* contribute to ovarian cancer risk?

Until recently it was thought that around 10–15% of ovarian, primary peritoneal, and fallopian tube cancers (referred to collectively as OC) were hereditary, with nearly all cases due to mutations in *BRCA1* and *BRCA2*, and some additional cases due to mutations in genes causing Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*). Newer studies have challenged that convention, demonstrating that around 20% of women with OC carry inherited mutations in OC susceptibility genes, and 20–25% of such mutations occur in genes other than *BRCA1* and *BRCA2* [7–10]. Lynch syndrome mutations are present in a small proportion of cases (<1%) [7,11], and the next most commonly mutated gene after *BRCA1* and *BRCA2* in OC patients is *BRIP1* (1.4% of cases) [7,9].

BRCA1 and *BRCA2* are part of the *BRCA*-Fanconi Anemia pathway, and other genes within this pathway such as *BRIP1*, *RAD51C*, and *RAD51D* have recently been implicated in hereditary OC [7,9,10,12–16]. These studies led the National Comprehensive Cancer Network (NCCN) to add guidelines to "consider" risk-reducing salpingo-oophorectomy, or RRSO, in women with mutations in these genes (Table 1) [17]. Recommendations for risk management for additional genes, such as *PALB2*, are currently controversial in that data on OC risk is conflicting, with some studies suggesting an association with OC [7,18–20] and some not [9,21]. In our study sequencing 1915 women with OC who were not selected by age or family history, we found that *PALB2* mutations were significantly more frequent in women with OC than in control populations, with odds ratios ranging from 4.4 to 10.2, depending on the control population [7]. Odds ratios for OC in these genes vs. cancer-free women over the age of 70 from the Women's Health Initiative (WHI) FLOSSIE cohort [22] are presented in Table 2.

It is equally important to understand which genes do not carry an increased risk of OC, for example, mutations in *CHEK2*, *RAD50*, and *MRE11A*, are equally frequent in women with OC and in control populations, indicating that they are not associated with an increased risk of OC [7,20]. While the Lynch syndrome genes are often lumped together for risk estimates, they are not equivalent. Mutations in *MHL1*, *MSH2*, and *MSH6* have been associated with an increased risk of OC [23–25], but mutations in *PMS2* have not been convincingly associated with OC risk [26,27]. Mutations in other genes such as *ATM*, *BARD1*, and *NBN* have been found in OC patients, in some studies more frequently than in controls [7,20,28], but risks are uncertain and more data is needed.

Many of these studies have had methodological features that impair precise risk estimates, including use of low sensitivity sequencing methods with inadequate depth and coverage and an inability to detect genomic rearrangements [9,10], use of public whole exome sequencing databases as a control group [7,20] (which include persons of both sexes and all ages and unknown phenotypes), and the use of women undergoing commercial gene panel testing as the source of OC cases [20,28]. Using a commercial testing population may be appealing due to the large sample size, however ascertainment bias and a lack of key clinical

https://doi.org/10.1016/j.ygyno.2018.12.003

Table 1
NCCN guidelines for selected OC risk genes.
(Adapted from NCCN guidelines version 2.2019, Genetic/Familial High-Risk Assessment: Breast and Ovarian [17].)

Gene	Ovarian cancer risk and management
BRIP1	Increased risk of ovarian cancer • Consider RRSO at 45–50 y
PALB2	Unknown or insufficient evidence for ovarian cancer risk
RAD51C	Increased risk of ovarian cancer • Consider RRSO at 45–50 y
RAD51D	Increased risk of ovarian cancer • Consider RRSO at 45–50 y

information such as histologic subtype or confirmation of invasive cancer hampers the ability to draw conclusions. While more work is needed, women with mutations in genes that have been associated with OC risk should be informed of current data and offered interventions to reduce the risk of OC, individualized to their personal situation.

3. Why should women with OC have genetic testing for inherited mutations?

OC has one of the highest proportions of cases attributable to inherited risk of any solid tumor, highlighting the importance of genetic testing for all women with invasive epithelial ovarian cancer. Identification of hereditary risk can help predict response to both traditional chemotherapeutics and novel therapies such as poly (ADP- Ribose) polymerase (PARP) inhibitors [29–32], and can inform patients of risk of other malignancies, such as breast carcinoma. The recent landmark SOLO-1 clinical trial demonstrated that women with OC and mutations in *BRCA1* and *BRCA2* had a 70% reduced risk of progression or death when receiving maintenance therapy with the PARP inhibitor olaparib after initial chemotherapy [33]. This dramatic benefit provides one of the more compelling reasons to identify these mutations early in the treatment course.

One of the main benefits of genetic testing is to identify cancer risk in unaffected family members who also carry the mutation. Lifetime risks of OC approach 50% for *BRCA1* and 20% for *BRCA2* [34,35]. Efforts at early detection of OC have been largely unsuccessful [36,37]. Therefore, for high risk women, experts recommend removal of the Fallopian tubes and ovaries (risk-reducing salpingo-oophorectomy, or RRSO) after completion of childbearing [17]. Surgical prevention dramatically reduces the incidence of OC in *BRCA1* and *BRCA2* mutation carriers, and improves all-cause mortality [38,39]. Increasing the proportion of women who can identify their genetic risk has dramatic potential to reduce mortality from OC.

4. Not enough women with OC are being tested

Despite the benefits of identifying inherited risk, most women with OC are still not undergoing genetic testing. A recent study that utilized the National Health Interview Survey estimated that approximately 11% of women with a prior diagnosis of OC had undergone genetic testing in the United States [40]. Potential barriers to obtaining genetic testing may include difficulty with access to genetic counseling, lack of knowledge regarding the benefits of testing, lack of referrals for testing, costs, and mistrust of the medical system. The need for genetic testing currently exceeds the availability of genetic counselors, and creative solutions will need to be explored. The Stand Up to Cancer Ovarian Cancer Dream team is conducting the MAGENTA (MAking GENetic Testing Accessible) trial, which has enrolled over 3000 subjects and will complete enrollment in late 2018 (NCT02993068). MAGENTA brings genetic testing directly to women at risk for hereditary ovarian cancer utilizing testing at home with a mailed kit, electronic results delivery, and telephonic genetic counseling. This and other ideas will have to be explored to determine the optimal strategies for improving access to testing.

5. Barriers to genetic testing are amplified in underserved populations

Minority women are underrepresented in cancer clinical trials and cancer genetics studies [41,42]. Black women with a personal or family history of cancers are less likely to undergo genetic counseling and genetic testing [43]. In a study of 92 mostly Black Medicare beneficiaries from the Southern Community Cohort Study, only 9% of breast and ovarian cancer patients meeting Medicare criteria for genetic testing had such testing [44]. Two institutional series from academic centers found that Black women with OC were 50–75% less likely to be referred for genetic counseling than White women with OC [45,46]. Approaches to increasing testing will need to be tailored to the specific needs of different groups, and further research is needed to determine effective strategies. Given these data on referral patterns, interventions to improve testing rates in Black women should include provider training in implicit bias and how that impacts health care decisions.

6. Should genetic testing strategies be more restrictive or more inclusive?

We should be offering germline genetic testing to all women with non-mucinous, invasive epithelial OCs. There is no evidence that only those with high-grade serous histology have inherited mutations, and mutations have been found in women with a variety of histological subtypes, including endometrioid, clear cell, undifferentiated carcinoma, low-grade serous, and carcinosarcomas [7,47]. As the costs of testing decrease and variant interpretation improves, there are few reasons to restrict access to genetic testing. In fact, some have proposed offering germline genetic testing to all women over the age of 30 [48], and there is data to suggest this would be cost effective compared to testing based on traditional criteria [49].

Sequencing OC neoplasms is also important, given that acquired (or somatic) *BRCA1* and *BRCA2* mutations also predict response to PARP inhibitors [29,31,50]. OC sequencing will detect many germline mutations in addition to somatic mutations, however the sensitivity of this method for germline mutation detection will vary depending on mutation type. For example, a germline mutation consisting of a single exon deletion is likely to be more difficult to identify in neoplastic versus germline DNA.

Table 2
Frequency of mutations in OC risk genes in OC cases vs. cancer-free women over the age of 70 (WHI).

Gene	Mutation frequency in OC ($N = 1915$)	Mutation frequency in WHI ($N = 6944$)	Cases vs. WHI Odds ratio (95% CI)	*P* value
BRIP1	26 (0.0136)	12 (0.0017)	8.0 (4.1–15.4)	<0.0001
PALB2	12 (0.0062)	7 (0.0010)	6.2 (2.6–16.5)	<0.0001
RAD51C	11 (0.0057)	5 (0.0007)	8.0 (2.8–20.8)	<0.0001
RAD51D	11 (0.0057)	5 (0.0007)	8.0 (2.8–20.8)	<0.0001

Mutation frequency in OC from Norquist et al. [7], mutation frequency in WHI controls from FLOSSIE project European American cohort [22].

Bioinformatics approaches to detecting germline and somatic mutations differ, and may be challenging to integrate by companies whose expertise lies with one or the other. Our University of Washington Department of Laboratory Medicine is currently offering tumor and germline sequencing in parallel using both tumor and blood samples (Soledad Jorge et al., unpublished data), allowing for simultaneous detection of germline and somatic mutations, with methods optimized for each approach. With the recent publication of SOLO-1 demonstrating a large benefit for PARP inhibitor maintenance therapy in the primary setting for women with advanced *BRCA*-mutated OC [33], identifying germline and somatic *BRCA1* and *BRCA2* mutations at the time of diagnosis is paramount and likely to be soon considered standard of care for optimal treatment planning.

7. Summary

We have come a long way since the 1990's in our understanding of inherited risk, and in the genetic testing options that are available to our patients. More research is needed to fully understand which genes are involved in inherited risk of OC, but these data are rapidly accumulating. Efforts must be made to improve access to genetic testing for all women with or at risk of OC, so that all can participate in the promise of precision cancer therapies and interventions to reduce the risk of OC. Increasing the identification of inherited risk offers one of our best hopes for reducing mortality from OC.

Conflict of interest

Dr. Norquist has nothing to disclose.

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