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Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions☆

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ABSTRACT

Women with germline mutations in the cancer susceptibility genes, *BRCA1* or *BRCA2*, associated with Hereditary Breast & Ovarian Cancer syndrome, have up to an 85% lifetime risk of breast cancer and up to a 46% lifetime risk of ovarian, tubal, and peritoneal cancers. Similarly, women with mutations in the DNA mismatch repair genes, *MLH1*, *MSH2*, *MSH6*, or *PMS2*, associated with the Lynch/Hereditary Non-Polyposis Colorectal Cancer (HNPCC) syndrome, have up to a 40–60% lifetime risk of both endometrial and colorectal cancers as well as a 9–12% lifetime risk of ovarian cancer. Mutations in other genes including TP53, PTEN, and STK11 are responsible for hereditary syndromes associated with gynecologic, breast, and other cancers. Evaluation of the likelihood of a patient having one of these gynecologic cancer predisposition syndromes enables physicians to provide individualized assessments of cancer risk, as well as the opportunity to provide tailored screening and prevention strategies such as surveillance, chemoprevention, and prophylactic surgery that may reduce the morbidity and mortality associated with these syndromes. Evaluation for the presence of a hereditary cancer syndrome is a process that includes assessment of clinical and tumor characteristics, education and counseling conducted by a provider with expertise in cancer genetics, and may include genetic testing after appropriate consent is obtained. This commentary provides guidance on identification of patients who may benefit from assessment for the presence of a hereditary breast and/or gynecologic cancer syndrome.

Introduction

The hallmarks of hereditary cancer syndromes include multiple affected family members, early age of onset, and the presence of multiple and/or bilateral primary cancers [1–4]. Although such clinical markers have long been recognized, it is now possible to identify some of the genetic alterations that predispose individuals to inherited breast, gynecologic and gastrointestinal cancers [5–11]. A recent study found that 24% of unselected ovarian cancers had a germline mutation, including 18% with a *BRCA1* or *BRCA2* mutation [12].

Women with mutations in the *BRCA1* cancer susceptibility gene associated with Hereditary Breast & Ovarian Cancer (HBOC) have a 65–85% risk for breast cancer and a 39–46% risk for ovarian, fallopian tube, or peritoneal cancer (Ov/FT/PC) by age 70 [13–15]. Similarly, women with mutations in *BRCA2* have risks of breast and Ov/FT/PC cancers by age 70 of approximately 45–85% and 10–27%, respectively.

Women with Lynch/Hereditary Non-Polyposis Colorectal Cancer (HNPCC) syndrome, caused by mutations in DNA mismatch-repair genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*), have increased risks for endometrial and ovarian cancers. For women with MLH1, MSH2 and MSH6 mutations, the lifetime risk of endometrial cancer is 20–54%, 21–49% and 16–71% respectively [16]. The lifetime risk of ovarian cancer for MLH1, MSH2 and MSH6 is 4–20%, 7.5–24% and 0–13.5% respectively [16–26]. PMS2 mutations are associated with a 15% lifetime risk of endometrial cancer and a small increased risk of ovarian cancer [27]. Women with Lynch syndrome also have a 25–50% lifetime risk of colorectal cancer, somewhat lower than their male counterparts [16].

☆ This document updates the earlier 2007 SGO statement on hereditary risk assessment and reflects emerging clinical advances and scientific advances in this period. Additional emphasis is placed on the increase in detection of germline mutations in ovarian cancer (which now includes ovarian, fallopian tube, and peritoneal cancer), detection of Lynch related endometrial cancers, and the new technologies which will allow for the detection of a greater number of germline mutations. The guidelines for referral of women for genetic counseling have been simplified and reflect current expanded recommendations including histopathology and clinical risk criteria in order to encourage greater detection of women with an inherited cancer predisposition, who may benefit from prevention strategies.

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Germline mutations in the PTEN gene, which underlies Cowden syndrome, have been associated with a 19–28% risk of endometrial cancer by age 70, however, in light of lack of censoring of endometrial cancer incidence rates for previous hysterectomy in these studies, the true risk may be higher in women with an intact uterus. In addition to endometrial cancer risk, women with germline mutations in the PTEN gene have up to a 50% risk of breast cancer and 3–10% risk of thyroid cancer [28–31]. Women who carry germline mutations in the TP53 gene, associated with Li Fraumeni syndrome, have up to a 60% lifetime risk of breast cancer, in addition to other "core" cancers that include sarcomas, brain, and adrenocortical carcinomas [32]. The less common Peutz–Jeghers syndrome, caused by mutations in STK11/LKB1 gene, is associated with elevated risk of cervical (adenoma malignum), ovarian (sex cord stromal tumors) and breast cancers (10%, 21%, and 50% lifetime risk, respectively) [33].

Although HBOC and Lynch are the most well-known syndromes associated with ovarian cancer, recently at least three new genes, including BRIP1, RAD51D, and RAD51C, have been described to be associated with a lifetime risk of 10–15% [12,34–36]. PALB2 mutations have been identified in breast and ovarian cancer families and unselected ovarian cancer cases though a clear increased relative risk has not been established [37,38]. Most recently, germline mutations in the DICER1 and SMARCA4 genes have been identified to be associated with Sertoli–Leydig tumors and ovarian small cell carcinoma, respectively [39–44]. It is expected that the list of genes associated with ovarian cancer will continue to increase in the very near future.

Evaluation for the presence of a hereditary cancer syndrome enables physicians to provide individualized and quantified assessment of cancer risk, as well as options for tailored screening and prevention strategies that may reduce morbidity associated with the development of malignancy. Strategies that have been demonstrated to improve outcomes in individuals at inherited risk include breast screening with magnetic resonance imaging (MRI) [45,46], colorectal cancer screening with colonoscopy [47], risk-reducing surgery, and chemoprevention (oral contraceptives for Ov/FT/PC risk). Though some studies suggest that tamoxifen, a selective estrogen receptor modulator, may reduce the risk of contralateral breast cancer in affected *BRCA1/2* mutation carriers [48,49], the limited sample size of the NSABP-P1 study, prohibits definitive conclusions from being drawn on its benefit to unaffected individuals.

It is estimated that in 2012 only 24% of newly diagnosed women with ovarian carcinoma in the United States received genetic testing for *BRCA1* and *BRCA2* mutations, despite current NCCN guidelines recommending genetic counseling and testing be offered to all women with this disease [50]. It is clear that only a small minority of women with an inherited predisposition to breast and Ov/FT/PC have been identified. Research has shown that women with an inherited mutation who have fallopian tubes and ovaries removed reduce their risk of ovarian cancer by over 90%, and also reduce their cancer-related and overall mortality [51]. In addition, *BRCA1* and *BRCA2*-related Ov/FT/PC are associated with improved survival, responsiveness to platinum chemotherapy and novel therapeutics such as PARP inhibitors [52]. Knowledge of genetic status will make a difference in the lives of patients and their families, both by prevention and therapy of associated cancers. Because of the direct impact on the care of the patient as well as the value of preventing cancer in family members, all women with epithelial ovarian cancer should receive genetic counseling and be offered genetic testing regardless of age or family history.

The Society of Gynecologic Oncology (SGO) is committed to encourageing the medical community to identify women who may benefit from assessment for the presence of a hereditary cancer syndrome.

Changing landscape of genetic testing

The June 2013 Supreme Court ruling was that "a naturally occurring DNA segment" (i.e., a gene) cannot be patented. This was a unanimous decision by the Court. Prior to this decision, Myriad Genetics held the patent on the *BRCA1* and *BRCA2* genes and therefore the vast majority of testing in the US was performed by their commercial testing facility at a cost of approximately $3000 and up to $4000 for the most comprehensive panel. The Court decided that specific proprietary methodology in genetic testing and also synthetically-generated strands of DNA, (called cDNA), are eligible for patent protection. Currently *BRCA1* and *BRCA2* testing can be obtained individually or as part of multiplex gene panels from a variety of commercial laboratories. Panels and testing technology vary with each laboratory but the expectation is that in the future, more panels of genes linked to risk will be available at a lower cost.

Several for-profit commercial entities now offer direct-to-consumer marketing of cancer risk panel tests, including the use of single nucleotide polymorphism (SNP) based tests. Cost for such a SNP-based analysis of saliva can run as low as $99. When measured at a population-level, risk-associated SNPs occur more commonly in those individuals with a condition than without; as such, they are considered to be associated with cancer but are not necessarily causative, and do not result in levels of risk that would currently alter clinical recommendations. Recently, the Consortium of Investigators of Modifiers of *BRCA1/2* (CIMBA) reported two new genetic risk modifiers (*BRCA1*-specific SNP rs4691139 and SNP rs17631303, located at 4q32.3 and 17q21.31, respectively), which increased the risk of ovarian cancer in both *BRCA1* and *BRCA2* mutation carriers [53]. Such findings may pave the way for further individualization of ovarian cancer risk assessment in *BRCA1/2* mutation carriers.

Our understanding of genetic predisposition for particular cancers is rapidly changing from individual genes and syndromes to multiplex testing for a number of cancer susceptibility genes to assess cancer risk. Such multiplex panels can be chosen based upon particular cancer patterns in families as well as suggested by ethnicity with certain inherited mutations more common in certain ethnic groups, e.g., Ashkenazi Jewish, French Canadians, Hispanic families. With the increase in complexity of testing technology, the uncertainty in the interpretation of the results and the range of potentially identifiable cancer-risk, the need for evaluating the likelihood of the presence of a hereditary cancer syndrome, choosing the appropriate test or panel, and interpreting the result, all clearly argue that the first step in patient assessment should be genetic counseling.

It is important to emphasize that assessment for the presence of an inherited cancer predisposition syndrome is a process that:

- Includes assessment of likelihood of the presence of a genetic predisposition to cancer, education and counseling;
- May include evaluation of available tumor, with testing including immunohistochemistry and microsatellite instability;
- Is conducted by a physician, genetic counselor or other providers with expertise in cancer genetics;
- May include germline genetic testing if desired after appropriate counseling and consent have been obtained.

This commentary provides guidance to physicians and other health professionals in the identification of patients who may benefit from assessment for the presence of an inherited predisposition for breast, ovarian and endometrial cancers.

These guidelines were developed through a series of face -to -face meetings and conference calls of the SGO Education Resource Panel for Hereditary Cancers, and updated through the SGO Clinical Practice Committee. The guidelines reflect the synthesis of a detailed literature review conducted by the panel's members as well as comments from gynecologic oncologists, general gynecologists, genetic counselors, medical oncologists and other gynecologic cancer professionals. The final recommendations were reviewed by the Clinical Practice Committee and the Publications Committee of the SGO, both of which provided valuable feedback prior to publication.

Recommendations

Given the potential impact on clinical care for both patients as well as their close family members, the SGO recommends that individuals