Hereditary gynecologic cancers

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1. Introduction

The present document has been developed by the FIGO Committee on Gynecologic Oncology to aid in the recognition of, and counseling and testing for inherited gynecologic cancers. Extensive consultation was conducted with the Committee and the FIGO Executive Board. This represents a consensus statement.

In the early 1990s, the molecular etiology of several hereditary cancers was established. The identification of specific genes associated with some cancers has allowed clinicians to more accurately assess hereditary cancer risk and establish screening and preventive interventions. Two of the best examples of this scientific discovery and increased awareness regarding gynecologic cancers are the discovery of the BRCA1 and BRCA2 genes and the identification of the molecular basis of the Lynch family cancer syndrome. The following paragraphs address the diagnostic, screening, and treatment issues associated with these syndromes.

2. Hereditary breast and ovarian cancer syndrome

Germline mutations in BRCA1 and BRCA2 account for the majority of families with hereditary breast and ovarian cancer syndrome. Although the reported incidence varies widely, approximately 10% of cases of ovarian cancer and 3%–5% of cases of breast cancer are due to mutations in the BRCA1 or BRCA2 genes [1–6]. However, a recent Australian study reported an overall incidence of 14% in over 1000 ovarian cancers screened and an incidence of almost 23% in high-grade serous cancers in the patient population [7]. In the general population, it is estimated that approximately 1 in 300 to 1 in 800 individuals carry a mutation in BRCA1 or BRCA2 [8]. A woman with a BRCA1 mutation has a 39%–46% risk of developing ovarian cancer, while a woman with a BRCA2 mutation has a 12%–27% risk. Furthermore, the estimated lifetime risk of breast cancer with a BRCA1 or BRCA2 mutation can be as high as 65%–74% [9–12]. For women with breast cancer, the 10-year actuarial risk of developing a subsequent ovarian cancer is 12.7% for BRCA1 mutation carriers and 6.8% for BRCA2 mutation carriers [13].

Ovarian cancers associated with BRCA1 and BRCA2 mutations have a distinct histologic phenotype. This type of cancer is predominantly of serous or endometrioid histology and is high grade. Mucinous and borderline ovarian cancers do not appear to be part of the tumor spectrum [14,15]. Primary fallopian tube cancer and primary peritoneal cancer are also part of the spectrum of disease associated with mutations in these genes [16,17].

Tailored screening and prevention strategies can reduce morbidity and mortality from breast and ovarian cancer, making it important to identify individuals at risk. Clinical criteria have been developed to assess patients with at least a 20%–25% chance of having an inherited predisposition to breast or ovarian cancer (Box 1). It is these patients for whom genetic risk assessment is strongly recommended. A second set of criteria is designed for those patients with greater than a 5%–10% chance of having an inherited predisposition to breast and ovarian cancer and for whom genetic risk assessment may be helpful [18] (Box 2). It should be noted, however, that these recommendations are not universal and this distinction is not made in a number of settings—in particular, in Germany and Australia.

More recent data indicate that, in the setting of a diagnosis of high-grade serous ovarian cancer, primary peritoneal cancer, or fallopian tube cancer, between 16% and 22% of unselected patients with a family history of these diseases will have a BRCA1 or BRCA2 mutation, while only 9% of patients without a family history of either breast or ovarian cancer will have a germline BRCA1 or BRCA2 mutation [7,19]. Given this prevalence of mutations, it is reasonable to consider hereditary risk assessment in any patient with high-grade serous ovarian cancer, primary peritoneal cancer, or fallopian tube cancer, especially if the results of such assessment could potentially have an impact on other family members. Testing for BRCA1 mutations should also include women with triple-negative breast cancer. A recent meta-analysis of 12 studies found that the relative risk of BRCA1 mutation in women with triple-negative breast cancer was 5.65 (95% confidence interval
Box 1
Criteria for genetic risk assessment for hereditary breast and ovarian cancer (>20%–25% chance of inherited predisposition).

- Patients with greater than a 20%–25% chance of having an inherited predisposition to breast and ovarian cancer and for whom genetic risk assessment is recommended:
  - Women with a personal history of both breast cancer and ovarian cancer.
  - Women with ovarian cancer and a first-degree relative with ovarian cancer or premenopausal breast cancer, or both.
  - Women with breast cancer at age 50 years or younger and a close relative with ovarian cancer or male breast cancer at any age.
  - Women of Ashkenazi Jewish ancestry with ovarian cancer.
  - Women of Ashkenazi Jewish ancestry in whom breast cancer was diagnosed at age 40 years or younger.
  - Any woman with high-grade serous ovarian, primary peritoneal, or fallopian tube cancer.
  - Women with a close relative with a known BRCA1 or BRCA2 mutation.
  - Women with a family history indicative of Lynch syndrome (hereditary nonpolyposis colon cancer) such as colon cancer—particularly if diagnosed before the age of 50 years—or endometrial, ovarian, gastric, or renal tract cancers.

*Criteria for the peritoneum and fallopian tubes should be considered as part of the spectrum of hereditary breast and ovarian cancer syndrome.*

[CI], 4.15–7.69), which was significantly higher than in women without triple-negative breast cancer [20]. Other criteria for testing are shown in Boxes 1 and 2.

Box 2
Criteria for genetic risk assessment for hereditary breast and ovarian cancer (>5%–10% chance of inherited predisposition).

- Patients with greater than a 5%–10% chance of having an inherited predisposition to breast and ovarian cancer and for whom genetic risk assessment should be strongly considered:
  - Women with breast cancer at age 40 years or younger.
  - Women with ovarian cancer, primary peritoneal cancer, or fallopian tube cancer of high-grade serous histology at any age.
  - Women with bilateral breast cancer (particularly if the first case of breast cancer was diagnosed at age 50 years or younger).
  - Women with breast cancer at age 50 years or younger and a close relative with breast cancer at age 50 years or younger.
  - Women of Ashkenazi Jewish ancestry with breast cancer at age 50 years or younger.
  - Women with breast cancer at any age and 2 or more close relatives with breast cancer at any age (particularly if at least 1 case of breast cancer was diagnosed at age 50 years or younger).
  - Unaffected women with a close relative who meets one of the previous criteria.
  - Women with triple-negative breast cancer (ER/PR negative, HER2 negative).

Women with BRCA1 or BRCA2 mutations should be offered risk-reducing salpingo-oophorectomy (RRSO) by age 35 years or when childbearing is complete [21,22]. Some countries recommend surgery at age 40 years or at an age 5 years younger than the youngest affected family member [23]. For bilateral RRSO, all tissue from the ovaries and fallopian tubes should be removed. Thorough visualization of the peritoneal surfaces with pelvic washings should be performed. Complete pathologic assessment that includes serial sectioning of the ovaries and fallopian tubes—at no more than 3-mm intervals—is necessary, with microscopic examination for occult cancer. Patients should also be counseled that they have a 2%–5% chance of having an occult cancer and a small residual risk of primary peritoneal cancer following RRSO.

2.1. Other risk reduction strategies

Combined oral contraceptives (COCs) may reduce the risk of ovarian cancer in women averse to risk-reduction surgery. In a case–control study of 670 women with BRCA1 mutations and 128 with BRCA2 mutations (including 1 patient with both), COC use reduced the risk of ovarian cancer in carriers of BRCA1 mutations (odds ratio [OR] 0.56 [95% CI, 0.45–0.71]; \( P = 0.0001 \)) and carriers of BRCA2 mutations (OR 0.39 [95% CI, 0.23–0.66]; \( P = 0.0004 \)) [24]. Similar findings were reported by Cibula et al. [25], who performed a meta-analysis on 3 case–control studies and showed a significant risk reduction for ovarian cancer in BRCA1 and BRCA2 mutation carriers with any past COC use and a significant trend by duration of COC use. For women with BRCA mutations, other strategies include CA-125 surveillance and transvaginal ultrasound; however, this approach does not enable detection of cancer at an early, curable stage and is not recommended [26–28]. Tamoxifen use in mutation carriers with breast cancer has been shown to reduce the risk of cancer in the contralateral breast by up to 53% but there are no published data on tamoxifen use and reduction in the incidence of ovarian cancer.

In 2007, Crum et al. [29] suggested that a subset of high-grade serous ovarian cancers arises from the distal fallopian tube, and coined the term tubal intraepithelial neoplasia (TIC). However, the etiologic significance of TIC in pelvic serous carcinoma is not yet known. Defining this is important because it may provide an additional means for risk-reducing surgery for pelvic serous carcinomas, particularly in women who carry BRCA mutations [30,31]. In fact, some have suggested routine removal of fallopian tubes during hysterectomy, even for benign disease, when childbearing is complete. Until more data become available, this approach should not be recommended as a routine.

3. Lynch syndrome

Lynch syndrome (or hereditary nonpolyposis colorectal cancer [HNPPC]) is caused by mutations in DNA mismatch repair genes (MLH1, MSH2, PMS2, or MSH6) [32]. For patients with HNPPC, the risks of developing endometrial and ovarian cancer by age 70 years are approximately 42%–60% and 9%–12%, respectively [33,34]. Women with HNPPC also have a 40%–60% lifetime risk of colorectal cancer. Genetic risk assessment for these hereditary cancer syndromes enables physicians to provide individualized and quantified assessment of risk, as well as options for tailored screening and prevention strategies that may reduce morbidity from these hereditary processes (Box 3). Strategies that may improve outcomes in individuals at inherited risk include colorectal cancer screening with colonoscopy [35] and risk-reducing surgery [36–40].

Hysterectomy with removal of both fallopian tubes and ovaries in women considered to be at high risk for ovarian cancer due to confirmed Lynch syndrome is associated with a decreased risk of developing endometrial and ovarian cancer and should be strongly considered when childbearing is complete.
Box 3
Recommendations regarding counseling and testing for Lynch syndrome (HNPCC).

Patients with greater than a 20%–25% chance of having an inherited predisposition to endometrial, colorectal, and related cancers and for whom genetic risk assessment is recommended:

- Patients with endometrial or colorectal cancer who meet the revised Amsterdam criteria, as listed below:
  - At least 3 relatives with a Lynch/HNPCC-associated cancer (colorectal cancer or cancer of the endometrium, small bowel, ureter, or renal pelvis) in 1 lineage.
  - One affected individual should be a first- or second-degree relative of the other 2.
  - At least 2 successive generations should be affected.
  - At least 1 HNPCC-associated cancer should be diagnosed before age 50 years.

- Patients with synchronous or metachronous endometrial and colorectal cancer, with the first cancer diagnosed prior to age 50 years.

- Patients with synchronous or metachronous ovarian and colorectal cancer, with the first cancer diagnosed prior to age 50 years.

- Patients with colorectal or endometrial cancer with evidence of a mismatch repair defect (i.e., MSI or immunohistochemical loss of expression of MLH1, MSH2, MSH6, or PMS2).

- Patients with a first- or second-degree relative with a known mismatch repair defect.

Abbreviations: HNPCC, hereditary nonpolyposis colorectal cancer; MSI, microsatellite instability.

4. General testing and counseling guidelines

It is important to emphasize that hereditary cancer risk assessment is a process that:

- Includes risk assessment, education, and counseling;
- Is conducted by a physician, genetic counselor, or other provider with expertise in cancer genetics;
- May include genetic testing if desired after appropriate counseling and after consent has been obtained.

Genetic testing for cancer predisposition requires informed consent that should include pre-test education and counseling concerning the risks, benefits, and limitations of testing, including the implications of both positive and negative genetic test results. Pre-test counseling should also include education on the limitations of current genetic testing technology, including the risks of false-negative results, as well as the uncertainties associated with genetic variants of unknown clinical significance. Individuals considering genetic testing should be aware that the potential risks of such testing include psychological stress and changes to family dynamics.

Risks may also include the potential for discrimination in health insurance or employment but there is little evidence that this has actually occurred to date [41,42].

Other factors that should be taken into account when counseling women include discussion regarding the management of menopausal symptoms and the use of hormone replacement therapy (HRT). Surgically induced menopause is often associated with more significant vaso-motor symptoms compared with natural menopause. Hormone replacement therapy appears to be effective in managing the symptoms of surgically induced menopause. In addition, there does not seem to be an increased risk of breast cancer in women who carry a BRCA mutation and who use HRT after RR50 performed before the age of 50 years compared with those who do not take HRT [43]. Women with a previous history of ER-positive breast cancer due to BRCA mutation should generally not be offered HRT after RR50. Primary peritoneal cancer may still occur in women who have undergone risk-reducing surgery.

Other inherited mutations can affect cancer risk in the female genital tract:

- Peutz–Jeghers syndrome, which is characterized by pigmented lesions on the lips/buccal mucosa and multiple gastrointestinal polyps due to STK11 mutation. Peutz–Jeghers syndrome is associated with ovarian sex cord-stromal tumors, adenoma malignum (minimal deviation adenocarcinoma), and lobular endocervical glandular hyperplasia.

- Cowden syndrome is characterized by the development of multiple hamartomas, distinctive dermatopathologic manifestations, and a predisposition toward various malignancies due to PTEN mutation, particularly endometrial cancer.

- Li–Fraumeni syndrome is characterized by a high frequency of multiple primary tumors, especially soft-tissue sarcoma. The syndrome is linked to germline mutations of the TP53 tumor suppressor gene and also increases the risk of breast cancer.

5. Summary points

- Cancer is a genetic disease that is either inherited or somatic.
- Mutations in BRCA1, BRCA2, and mismatch repair genes (Lynch syndrome) can be identified by genetic testing [18] (Boxes 1 and 2).
- Genetic counseling is important for patients with suspected inherited risk and should be recommended before testing.
- Once a mutation is identified, the patient should be counseled regarding risk-reducing surgery, other risk-reduction strategies, and altered screening.
- Inherited cancer risk affects other family members, and counseling with testing should be recommended for other family members who are at risk.

Conflict of interest

L.D. and N.B. have received honoraria for appearing on various speaker forums about HPV vaccination and have received research support from GlaxoSmithKline and MSD/Merck for HPV-related research. The other Committee members have no conflicts of interest.

References

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