International Journal of Gynecology and Obstetrics 124 (2014) 189–192

Contents lists available at ScienceDirect

International Journal of Gynecology and Obstetrics

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

FIGO GUIDELINES

Hereditary gynecologic cancers ☆

David Mutch *, Lynette Denny, Michael Quinn; for the FIGO Committee on Gynecologic Oncology [1]

ARTICLE INFO

Keywords:
BRCA1 and *BRCA2*
Breast cancer
Genetic risk assessment
Germline mutations
Intensified early cancer detection
Ovarian cancer
Prophylactic surgery
Screening and prevention

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

☆ These guidelines were approved by the FIGO Executive Board on November 11, 2013.

* Corresponding author at: Division of Gynecologic Oncology, 4911 Barnes Jewish Hospital Plaza, Washington University School of Medicine, St Louis, MO 63110, USA. Tel.: +1 314 362 3181; fax: +1 314 362 2893.
E-mail address: mutchd@wudosis.wustl.edu (D. Mutch).

[1] Committee members: H. Belhadj (Switzerland), J. Berek (USA), A. Bermudez (Argentina), N. Bhatla (India), J. Cain (USA), L. Denny (Chair; South Africa), K. Fujiwara (Japan), N. Hacker (Australia), E. Åvall-Lundqvist (Sweden), D. Mutch (USA), F. Odicino (Italy), S. Pecorelli (Italy), J. Prat (Spain), M. Quinn (Co-chair; Australia), M.A-F. Seoud (Lebanon), S.K. Shrivastava (India).

http://dx.doi.org/10.1016/j.ijgo.2013.12.001

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 [a].
- 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 [a] 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.

[a]Cancer of 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 [HNPCC]) is caused by mutations in DNA mismatch repair genes (*MLH1*, *MSH2*, *PMS2*, or *MSH6*) [32]. For patients with HNPCC, the risks of developing endometrial and ovarian cancer by age 70 years are approximately 42%–60% and 9%–12%, respectively [33,34]. Women with HNPCC 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.