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SEOM clinical guidelines for hereditary cancer

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Abstract Research in genetics has facilitated the identification of highly penetrant genes responsible for a large number of diseases. In the oncology field, genetic counselling and gene testing are focused on the two most common syndromes in familial cancer: hereditary breast and ovarian cancer syndrome (HBOC) and hereditary non-polyposis colorectal cancer or Lynch syndrome (LS). The objective of this guideline in hereditary cancer is to summarise the current state of knowledge and make recommendations in the areas of diagnosis, prevention and treatment of hereditary cancer.

Keywords Hereditary cancer · *BRCA1* · *BRCA2* · Lynch syndrome

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Hereditary breast and ovarian cancer syndrome

Introduction

Breast cancer (BC) is the most prevalent type of malignant tumour in women in the European Union, affecting up to 8% of those who live to age 75. A positive family history is a significant risk factor reported by 15–20% of women with BC. Moreover, 5–10% of all breast cancers are associated with an inherited gene mutation.

Approximately 3–5% of breast cancer cases and 10% of ovarian cancer cases can be traced to germline mutations in *BRCA1* and *BRCA2* genes. Hereditary breast and ovarian cancer syndrome (HBOC) is the most relevant inherited cancer-susceptibility syndrome, characterised by multiple cases of breast and/or ovarian cancer in the same individual or close blood relatives, either maternal or paternal.

Assessment of an individual's risk of HBOC is based on a careful evaluation of the family history. Characteristics indicative of HBOC include onset of the disease at an early age, bilaterality, ancestry (e.g., Ashkenazi Jewish), male BC and family history of breast and/or ovarian cancer. Genetic counselling and testing are increasingly being integrated into the management of women at risk for BC and/or ovarian cancer (OC). These women benefit from screening/prevention strategies to reduce their risks.

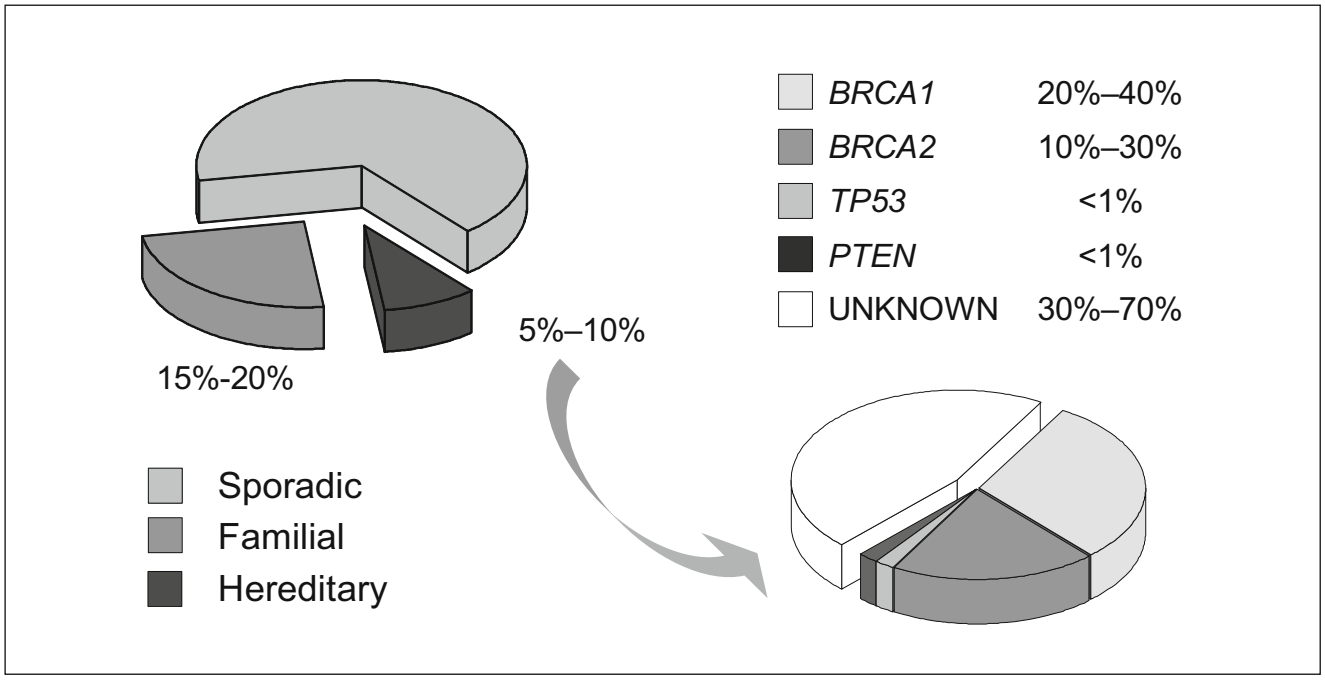

Fig. 1 Causes of hereditary susceptibility to breast cancer. **a** Percentage of sporadic, familial and hereditary breast cancer cases diagnosed in the general population. **b** Frequency of mutations found in major susceptibility genes in hereditary breast cancer cases

Other hereditary BC syndromes, caused by mutations in highly penetrant genes, account for less than 1% of all cases of breast cancer: Li-Fraumeni syndrome *(TP53)*, PTEN-hamartoma syndrome *(PTEN)*, Peutz-Jeghers syndrome *(LKB1/STK11)* and hereditary diffuse gastric cancer syndrome *(CDH1/E-cadherin)* (Fig. 1).

BRCA1 and BRCA2 mutations and cancer risk

Lifetime risk of cancer

The probability of cancer development is variable in carriers of *BRCA1/2* mutations even within the same family. A recent meta-analysis indicates that cumulative risks by age 70 are as follows: breast cancer risk of 57% (95% CI: 47–66%) for *BRCA1* and 49% (95% CI: 40–57%) for *BRCA2* mutation carriers; and ovarian cancer risk of 40% (95% CI: 35–46%) for *BRCA1* and 18% (95% CI: 13–23%) for *BRCA2* [1]. Similar results have been published for the Spanish population [2] (Fig. 2).

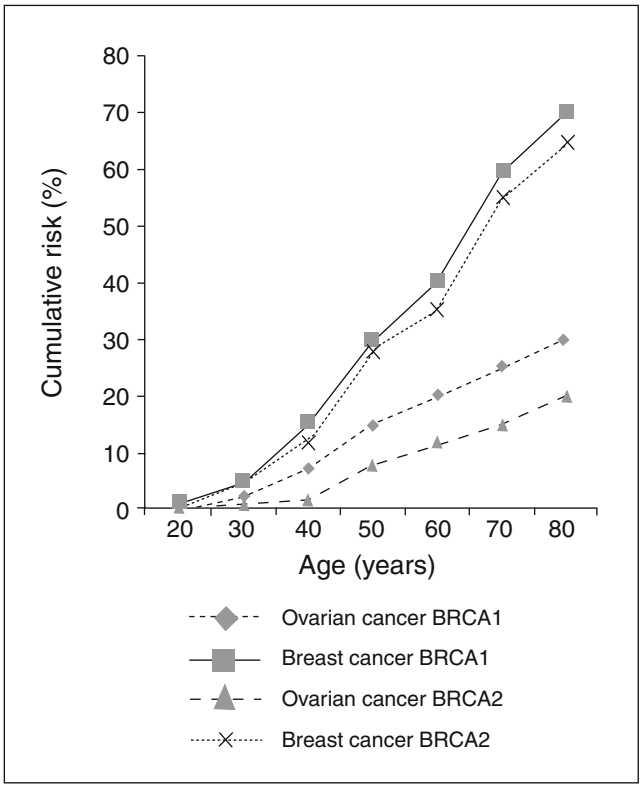

Fig. 2 Average cumulative risk of ovarian/breast cancer in carriers of *BRCA1/2* mutations

Risk of associated tumours and second malignancies

A hallmark of hereditary cancer is the predisposition toward multiple primary cancers. The risk of contralateral BC is significantly increased in *BRCA1* and *BRCA2* carriers compared with controls with an estimated 10-year risk ranging from 18 to 28% vs. 5 to 6%, respectively [3]. A significant concern for *BRCA1/2* breast cancer survivors is the threat of developing ovarian cancer; the 10-year actuarial risk of OC in such patients was 12.7% and 6.8% for positive carriers, respectively. Ovarian cancer was the cause of death in one-quarter of the patients *BRCA1/2* positive with stage I breast cancer [4]. Importantly, primary fallopian tube cancer and primary peritoneal cancer, although

Table 1 Criteria for genetic testing in hereditary breast and ovarian cancer syndrome

- Families with 3 or more breast and/or ovarian cancer cases in the same paternal o maternal lineage
- Families with 2 affected members with breast and/or ovarian cancer and at least one of the following characteristics:
  - Male with breast cancer or
  - History of ovarian cancer/fallopian tube/primary peritoneal or
  - Both breast cancer diagnosed prior to age 50 or
  - One of them is bilateral and the other <50 years
- Families with 1 affected member with breast and/or ovarian cancer if:
  - Women with a personal history of breast and ovarian cancer
  - Women with breast cancer diagnosed at age 30 or younger
  - Women with bilateral breast cancer diagnosed < 40 years
- Known deletereous mutation identified in the family

rare, are also part of the tumour spectrum of HBOC. *BRCA2* mutations carriers have been reported to have a higher risk of pancreatic cancer. Male carriers of a germline mutation (especially in *BRCA2*) have a greater risk of prostate and breast cancer [5].

Phenotypic expression of hereditary breast/ovarian cancer

BRCA1 breast cancer is more likely to be characterised as "triple negative" (ER–PR–HER2–) than sporadic cases. Therefore, individuals with early-onset triple-negative BC may consider genetic testing, especially if there is a family history of cancer [6]. The histology patterns of *BRCA2* breast cancer appear to be more heterogeneous. The histology of ovarian cancers in *BRCA1/2* carriers is more likely to be serous high-grade adenocarcinoma compared with those cases in non-carriers.

Risk assessment and counselling

Individuals at risk for breast and/or ovarian cancer should be referred for genetic counselling, a multistep process that includes: cancer risk assessment, education, evaluation of patient's needs and concerns, psychosocial support and genetic testing in selected cases. Potential benefits, limitations and risks of gene tests are important considerations in the decision-making process. Outcomes should be discussed with patients, including true-positive, true-negative and uninformative test results. A clear distinction should be made between the probability of being a mutation carrier and the probability of developing a cancer. When the familial mutation is unknown, the affected member with the highest likelihood of carrying a *BRCA1/2* mutation should be tested. If more than one is affected, first consider male breast cancer, ovarian cancer, youngest age or bilateral disease.

Before testing, patients should be aware of options for prevention, surveillance and treatment. For those individuals who choose not to proceed with testing, recommendations should be adjusted for primary and secondary prevention according to personal and family history

Clinical criteria for testing

The selection of appropriate candidates for genetic testing is based on personal and pedigree characteristics that determine an individual's prior probability of being a mutation carrier. Clinical criteria have been developed to identify patients who benefit from genetic risk assessment (Table 1). Moreover, some statistical models (e.g., BOADICEA, BRCAPRO) have been developed to estimate the likelihood that a *BRCA1/2* mutation is present.

Follow-up and risk-reduction strategies for mutation carriers (Table 2)

The role of lifestyle habits in the risk of BC in carriers of *BRCA1/2* mutations is not well defined. Regular physical exercise, obesity avoidance and breastfeeding appear to

Table 2 Management of women at risk of hereditary breast and/or ovarian cancer syndrome

- Regular monthly breast self-exam (BSE) starting at age 18
- **Semianual clinical breast exam** starting at age 25
- **Annual mammogram and breast MRI screening** starting at age 25 or individualized based on earliest case of breast cancer in the family
- **Risk-reducing salpingo-oophorectomy** after completion of child bearing, between 35-40 years old/or individualised based on family history
- **Risk-reducing bilateral mastectomy**
- For those not interested in risk-reducing salpingo-oophorectomy consider transvaginal ultrasound + Ca 125 every 6 months starting at age 35 or 5-10 years earlier than the earliest ovarian cancer in the family
- Chemoprevention strategies for breast and ovarian cancer
- Reproductive options

Words in bold identifies the main recommendations in HBOC

modestly reduce the risk of breast cancer in *BRCA1/2*-positive individuals [7].

Ovarian and fallopian tube cancers

Risk-reducing surgery: The absence of reliable methods for early OC detection, the poor prognosis of advanced disease and mortality reduction reported in mutation carriers that performed a risk-reducing bilateral salpingo-oophorectomy (RRSO) have lent support for the performance of this risk-reducing surgery [8–10]. A recent prospective multicentre cohort study showed that for *BRCA1/2* mutation carriers RRSO was associated with a lower risk of ovarian cancer, close to 70% in those without breast cancer and 85% in those with a prior BC diagnosis. Furthermore, RRSO in *BRCA1/2* carriers was associated with a lower risk of a first diagnosis of breast cancer, all-cause mortality, and breast and ovarian cancer-specific mortality [9]. RRSO should be performed between 35 and 40 years of age or upon completion of childbearing. It should be taken into account that *BRCA1* mutation carriers are more likely than *BRCA2* carriers to develop ovarian cancer before the age of 50. Peritoneal washings should be done at surgery, and pathologic assessment should include fine sectioning of the ovaries and fallopian tubes.

Surveillance: For individuals who have not elected RRSO, periodic screening with CA-125 biomarker and transvaginal ultrasound could be recommended starting between 30 and 35 years of age (or 5–10 years before the earliest OC in the patient's family). Patients should be informed that ovarian screening is neither an effective strategy for early detection nor an option for mortality reduction from OC. Therefore, screening is not a reasonable substitute for RRSO.

Chemoprevention: Studies have reported a substantial reduction of ovarian cancer risk in *BRCA1/2* mutation carriers who took oral contraceptives for more than 3 years. However, other studies have suggested that oral contraceptives increase the risk of breast cancer in *BRCA1/2*-positive women, especially if used for 5 or more years. Physicians should discuss the risks and benefits of chemoprevention with oral contraceptives in *BRCA1/2* carriers [11].

Breast cancer

Surveillance: Monthly breast self-examination should begin by age 18 and clinical/radiological breast examinations by age 25. Annual breast magnetic resonance imaging (MRI) should be performed in high-risk women (*BRCA1/2* carriers or those with a BC lifetime risk greater than 20–25%) as an adjunct to mammography. Overall, studies have found high sensitivity for MRI, ranging from 71% to 100% vs. 16% to 40% for mammography in high-risk women. Women should be informed about the benefits, limitations and potential harms of screening, including the likelihood of false-positive and false-negative findings [12].

Risk-reducing surgery: Bilateral risk reduction mastectomy (RRM) has been shown to reduce the risk of breast cancer by at least a 90%, depending on the type of mastectomy procedure [13]. Physicians should discuss the option of RRM in multidisciplinary consultations regarding not only the degree of protection but also its potential complications and psychosocial effects.

RRSO is also associated with a statistically significant reduction of 37% in the risk of BC in *BRCA1* and 64% in *BRCA2* mutation carriers [9]. This protection could be limited to patients who are premenopausal at the time of surgery. An optimal age for RRSO is difficult to specify and risk of osteoporosis and cardiovascular disease associated with premature menopause should be addressed with respect to RRSO procedure. Hormone replacement therapy (HRT) could be considered with caution in selected cases. Clinical studies are needed to evaluate the safety and efficacy of HRT after RRSO.

Chemoprevention: Limited data from the NSABP-P1 study suggest that chemoprevention with tamoxifen may reduce the risk of BC by 62% in women with *BRCA2* mutations, but not in *BRCA1* carriers [14]. Actually, chemoprevention should be offered in the context of clinical trials to *BRCA1/2* carriers.

Male carrier management

Male positives for *BRCA1/2* mutations should have clinical follow-up and undergo training in regular breast self-exam. Mammography should be only considered when clinically indicated. Involvement in population screening guidelines for prostate cancer could be recommended.

Reproductive options

Counselling on reproductive options such as prenatal techniques and pre-implantational genetic diagnosis should be

Table 3 Amsterdam criteria (AC)

- There should be at least three relatives with colorectal cancer (CRC) or other a Lynch syndrome-associated tumour[a]: (AC type I include only CRC; AC type II include all the cancers listed)
- One relative should be a first-degree relative of the other two
- At least two successive generations should be affected
- At least one tumour should be diagnosed before the age of 50 years
- Familial Adenomatous Polyposis should be excluded in CRC cases
- Tumours should be verified by histopathological examination

[a]Lynch syndrome-related tumours include colorectal, endometrial, stomach, ovarian, pancreas, ureter, renal pelvis, biliary tract and brain tumours, carcinoma of the small bowell, sebaceous gland adenomas and keratoacanthomas

Table 4 Revised bethesda guidelines (BG)

1. CRC diagnosed in a patient <50 years
2. Presence of synchronous, metachronous colorectal or other Lynch syndrome-related tumours[a], regardless of age
3. CRC with high MSI phenotype diagnosed in a patient aged <60 years
4. Patient with CRC and a first-degree relative with a Lynch syndrome-related tumour[a], with one of the cancers diagnosed at age <50 years
5. Patient with CRC with two or more first-degree or second-degree relatives with a Lynch syndrome-related tumour[a], regardless of age

[a]Lynch syndrome-related tumours include colorectal, endometrial, stomach, ovarian, pancreas, ureter, renal pelvis, biliary tract and brain tumours, carcinoma of the small bowell, sebaceous gland adenomas and keratoacanthomas

addressed with those couple interested. Risk of a rare Fanconi anaemia risk should be discussed with *BRCA2* mutation carriers, especially in populations with founder mutations.

Management of high-risk women without identified BRCA *mutations*

On average, more than 70% of HBOC families are negative for *BRCA1/2* germline mutations, considering these results as uninformative. The ability to quantify cancer risks in uninformative high-risk families is hampered by limited research. Women with a significant lifetime risk of breast cancer (>20–25%) who test negative for *BRCA1/2* should consider high-risk BC management. However, studies suggest that women from *BRCA1/2* mutation-negative site-specific breast cancer families are not at increased risk for ovarian cancer. Therefore, no further measure on reducing OC risk is needed [15].

Lynch syndrome (LS)

Introduction

Lynch syndrome (LS) is the most common hereditary form of colorectal cancer (CRC). Its prevalence is 2–5% of all newly diagnosed patients with CRC [16]. LS is an autosomal dominant disorder caused by germline mutations in at least four DNA mismatch repair (MMR) genes (*MLH1, MSH2, MSH6, PMS2*), which lead to a characteristic tumour phenotype: microsatellite instability (MSI) and loss of MMR protein expression. Lifetime cancer risk related to LS is 24–75% for CRC (proximal colonic cancer predilection, mean age 45 years), 27–71% for endometrial adenocarcinoma (mean age 50 years), 3–13% for ovarian carcinoma, 2–13% for gastric carcinoma, 1–12% for urinary tract cancer, 1–4% for brain gliomas, 2–4% for bile duct/gallbladder/pancreatic cancer and 4–7% for small bowel cancer [16]. Muir-Torre variant includes sebaceous gland adenomas and keratoacanthomas.

Diagnosis

Molecular diagnostics of LS is a process that can combine several phases. Interpretation of the results can be complex and the data should be discussed together by a multidisciplinary team [17].

Selection of individuals for LS

Family history, clinical and pathologic features of the tumours, may raise a suspicion that LS is present. Patients should be referred for genetic counselling in a familial cancer clinic when clinical criteria are met (Tables 3 and 4). In newly diagnosed CRC from the general population, the revised Bethesda guidelines (BG) have a 72–100% sensitivity to identify carriers of a deleterious mutation in MMR genes [18, 19]. Revised BG are recommended for selecting individuals suspected of LS that require further tumour molecular evaluation. It should be considered that 5–9% of endometrial cancer patients younger than age 50 years have been found to carry LS-associated mutations (mainly MSH2 mutations) [20]. Statistical models may also help elect individuals and guide the molecular evaluation (i.e., PREMM1,2,6; MMRPro, MMRpredict) [21].

Evaluation of the tumour

Clinical selection of patients along with molecular evaluation of CRC (MSI testing and immunohistochemistry (IHC)) are recommended as a highly effective diagnostic strategy [19]. The negative predictive value of these studies is important (99.7%): microsatellite stability (MSS) and normal MMR protein expression often rule out LS. In this setting, when Amsterdam criteria are met and more than one CRC tumour has been studied to exclude a phenocopy, familial colorectal cancer type X (FCC-X) diagnosis can be made [22]. Loss of MSH2, MSH6 or PMS2 protein and MSI may establish the diagnosis of a DNA MMR-defective tumour, even without finding a pathogenic mutation.

It should be noted that 10–15% of sporadic CRC may show MSI secondary to MLH1 gene promoter hypermethylation. In these cases, the analysis of the V600E mutation in BRAF gene or the study of the MLH1 promoter hypermethylation may help to detect sporadic tumours, whereas negative results of these tests can often lead to diagnose LS.

MMR mutation testing

Once a DNA MMR-defective tumour is identified, MMR mutation testing (full gene sequencing and large rearrangements study) finds a pathogenic mutation in more than 60% of patients. A pathogenic mutation confirms LS and allows pre-symptomatic diagnosis. IHC directs genetic testing to the specific MMR gene for which expression is lost and

Table 5 Recommended screening protocol for Lynch syndrome and familial clustering of colorectal cancer

Disorder	Lower age limit (years)	Examination	Interval (years)
Lynch syndrome	20-25	Colonoscopy	1-2
	30-35	Gynecological examination, transvaginal ultrasound, aspiration biopsy	1-2
	30-35	Gastroduodenoscopy[a]	1-2
	30-35	Abdominal ultrasound, urinalysis and cytology urine[b]	1-2
FCC-X and other familial clustering of colorectal cancer case in the family	45 or 5-10 years before the youngest case	Colonoscopy	3-5

[a]If gastric cancer is present in the family or in countries with high incidence of gastric cancer
[b]If urinary tract cancer is present in the family
FCC-X, familial colorectal cancer type X

most likely mutated. Hypermethylation of the promoter of germline *MLH1* and the hypermethylation of the *MSH2* promoter secondary to *EPCAM* gene deletion have recently been described as causes of LS.

Recommendations

Increased risk for cancer in LS deserves medical management involving surveillance and risk-reducing measures (Table 5). A careful discussion of the risks, benefits and limitations of the procedures is advisable.

Intensive colonoscopic screening reduces CRC incidence by 63% and improves overall and CRC-related survival [23]. Colonoscopic surveillance every 1–2 years, starting between the ages of 20 and 25, is recommended for patients with LS. Chromoscopic colonoscopy and narrow band imaging may improve the detection of polyps. For patients with unresectable adenomas or cancer by colonoscopy, and for those unable to follow a screening programme, subtotal colectomy is a choice to be considered.

For FCC-X and other families with clustering of CRC, enhanced colonoscopic surveillance is recommended every 3–5 years beginning 5–10 years before the youngest case in the family or at age 45 years.

Annual endometrial sampling and ovarian transvaginal ultrasound, beginning between age 30 and 35, are usually recommended for women with LS but evidence is insufficient regarding early detection of ovarian cancer and reduction in mortality. Prophylactic hysterectomy and bilateral salpingo-oophorectomy can be offered as an option for cancer prevention to women aged 35 years or older who do not want to preserve fertility, since it substantially reduces site-specific cancer [24], although evidence on reduction in cancer-related mortality is lacking.

Screening for uncommon cancers integral to LS varies depending on specific family history. It is an empirical, not validated, approach that should be addressed by a genetic counsellor. When there are urologic tumours, urinalysis with cytology and renal echography every 1–2 years, beginning at 25–35 years, may be recommended. If gastric cancer runs in the family, upper gastrointestinal tract endoscopy can be offered periodically. Imaging of the abdomen may also be considered in some instances.

Conflict of interest The authors declare that they have no conflict of interest relating to the publication of this manuscript.

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