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Review

Practical aspects of genetic counseling in breast cancer: Lights and shadows

Alexandre Christinat [a], Olivia Pagani [a,b,*]

[a] Institute of Oncology of Southern Switzerland (IOSI), Bellinzona, Switzerland
[b] Genetic Counseling Service IOSI, Lugano, Switzerland

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ABSTRACT

In unselected populations, less than 10% of breast cancers are associated with germline mutations in predisposing genes. Breast cancer type 1 and 2 (*BRCA1* and *BRCA2*) susceptibility genes are the most common involved genes and confer a 10–30 times higher risk of developing the disease compared to the general population. A personal or family history suggestive of inherited breast cancer syndrome may be further evaluated to assess the risk of genetic predisposition and the presence of a genetic mutation. Breast cancer genetic counseling should include a careful risk assessment with associated psychosocial evaluation and support, possible molecular testing, personalized discussion of results. Knowledge of *BRCA* status can influence individualized cancer risk-reduction strategies. i.e. active surveillance, prophylactic surgery and/or pharmacoprevention.

Introduction

Carcinogenesis is a multistep process involving genetic alterations.[1] Sporadic mutations can occur in somatic or germline cells while hereditary or familial cancers result of one or more mutations in parental germline cells. Breast cancer (BC) is the most common cancer in women.[2] Many risk factors have been associated with breast and ovarian cancer (OC): a powerful disease predictor is the inheritance of a mutation in one of the tumor suppressor *BRCA1* and *BRCA2* genes, which interact with other genes and environmental/lifestyle factors.

Genetic cancer risk assessment and counseling allow to identify individuals at increased risk for hereditary cancer: it's a multi-step process, which includes the evaluation of personal and family history, calculation of gene mutation probability, discussion of genetic testing cost/benefit and test results, surveillance planning, cancer reduction strategies and psychosocial support including reproductive decision making, employment/insurance considerations and protection from genetic discrimination.

Several models have been developed in countries with different social, economical and cultural backgrounds, within different health systems. Many health-care professionals are involved (genetic counsellor, geneticist, psychologist, medical oncologist, gynaecologist, breast surgeon, general practitioner, oncologic nurse, social worker) in a multidisciplinary approach.

The present review illustrates the different steps and challenges of genetic counseling for hereditary BC.

BRCA1 and BRCA2 genes and related syndrome

BRCA1 and *BRCA2*, identified in 1994 and 1995, are high-penetrance BC susceptibility genes involved in DNA repair and DNA damage response.[3,4] *BRCA1* is located on chromosome 17q21: through interaction with a number of genes it is implicated in 1) double-strand break repair, 2) cell cycle checkpoint activation, which allows cells to repair damage before progressing to mitosis, 3) DNA damage response activation. *BRCA2*, located on chromosome 13q, is involved in repair of replication-mediated double-strand DNA breaks. Germline mutations in *BRCA1* or *BRCA2* predispose to the breast and ovarian cancer (HBOC) syndrome. Due to the autosomal pattern of inheritance, siblings and offspring of a mutation carrier have a 50% chance of inheriting the predisposing mutation. Mutations take place through the entire coding region with over 2000 different mutations isolated so far.

BRCA1/*BRCA2* mutations occur in about 1 of 300–500 individuals in the general population but mutation prevalence varies among ethnic groups and geographic areas and may be influenced by the so-called founder mutations ("founder effect"), i.e. a mutation frequently observed in a population derived from a small ancestral group, geographically or culturally isolated, in which one or more founders was a carrier of the mutant gene.[5] Founder mutations were identified among Ashkenazi Jews (AJ) and in different populations from Canada, Hungary, Sweden, Netherlands and Italy.[6] As an example, one of the three major mutations in the AJ

* Corresponding author. Institute of Oncology of Southern Switzerland (IOSI), Bellinzona, Switzerland.
E-mail address: alexandre.christinat@eoc.ch (A. Christinat).

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population occurs in 1 of 40 subjects as compared to 1 of 400 individuals in the general population. A well-studied founder mutation (*BRCA2* 999del5) was identified in Iceland: the truncated form of BRCA2 was found in 0.4% of unaffected Icelanders and in 7.9% and 8.5% of breast and ovarian cancer patients, respectively.[7]

The mean cumulative BC risk for mutation carriers at age 70 was 57% (95% CI, 47–66%) for *BRCA1* and 49% (95% CI, 40–57%) for *BRCA2* mutation carriers in a high-risk population-based meta-analysis of ten studies.[8] In addition, the mean age of BC diagnosis tends to be younger for *BRCA1* than *BRCA2* mutation carriers (43 vs 47 years respectively).[9–11] Patients with *BRCA1/2* mutations have also an increased risk of contralateral BC, of approximately 3% per year.[12]

Male BC is also characteristic of the *BRCA2* phenotype. The lifetime risk of male BC in *BRCA2* mutation carriers is approximately 80–100 times higher than in the general population and *BRCA2* mutations account for roughly 15% of all male BC.[13]

BRCA1/*BRCA2* mutation carriers have also an elevated risk of other malignancies.[8] Overall, women with HBOC syndrome have a 15–40% lifetime risk of developing OC (25–65% in *BRCA1*-, 15–20% in *BRCA2* carriers). Increased risk of pancreatic cancer was reported both for BRCA1 but especially for BRCA2 carriers (relative risk 2.26 and 3.51, respectively). An elevated relative risk of prostate cancer was also demonstrated for *BRCA2* carriers (up to 20-fold increase), particularly in men aged <65 years, but the actual frequency of patients who develop the disease is apparently low (0.1%).[14–18]

BRCA1-related BC are predominantly triple negative (i.e. estrogen and progesterone receptor-negative and human epidermal growth factor 2 (HER2) receptor-non amplified).[19,20] In addition, *BRCA1* mutation occurs in about 1 of 4 patients with triple negative BC.[21,22] *BRCA2*-mutated patients show the same range of molecular subtypes as in sporadic BC (Table 1).

Other hereditary syndromes (Table 2) associated with an increased risk of BC/OC include Lynch (also known as hereditary non-polyposis colorectal cancer [HNPCC]), Peutz-Jeghers and Ataxia Telangiectasia syndromes. Germline mutations in the *TP53* and *PTEN* genes are found in Cowden and Li-Fraumeni syndromes, respectively, and are also associated with an increased risk of BC.

Nearly 2000 unique mutations have been identified throughout both of these large genes. Ideally, mutation analysis in a family should begin with someone diagnosed with BC/OC to maximize the chances of identifying the familial mutation and of accurately interpreting test results in other family members. Without the mutation identified in an affected individual (or another relative), interpretation of a wildtype *BRCA* genotype in a family member as a "true negative" cannot be ruled out, as several other explanations exist. If the affected individual is deceased, the only materials available for genetic analysis may be archived pathological specimens. Unfortunately, extraction from formalin-fixed paraffin-embedded (FFPE) tissue yields less and more fragmented DNA than that extracted from frozen tissue or blood specimens. This lower quality DNA is not adequate to complete nucleotide sequencing of large genes or rearrangement analysis. Founder mutations have recently been successfully detected in FFPE specimens and saliva.[23,24]

Genetic testing is also complicated by the fact that penetrance of *BRCA* genes is highly influenced by other factors such as modifier genes, response to DNA damage, and environmental factors (i.e. exposure to carcinogens, hormonal/reproductive factors).

In addition, new BC susceptibility genes have been identified that confer smaller cancer risk than *BRCA1/2*: a specific mutation (1100delC) in *CHEK2*, a gene activating *p53* and *BRCA1* in response to DNA damage, causes approximately a 2-fold increased risk for female BC and a 10-fold increased risk for male BC, accounting for 1% female and 9% male BC overall.[25] Routine testing for *CHEK2* is still controversial: due to its lower frequency and smaller impact on BC risk, newer strategies when counseling women with this mutation should be developed.

Table 1
Characteristics of *BRCA1* and *BRCA2* associated cancer.

Phenotype	BRCA1	BRCA2
ER expression	Negative in 80%	Positive in 60%
PR expression	Usually negative	Mostly positive
ERBB2 amplification	Usually negative	10% amplified
Onset of disease	Between 30 and 50 years	Between 40 and 70 years
Associated malignancies	Lifetime risk	
Breast	47–66%	40–57%
Ovarian	35–46%	13–23%
Pancreas	<10%	<10%
Prostate	Elevated in Ashkenazi	35–40%

Table 2
Selected hereditary syndromes associated with an increased risk of BC.

Syndrome	Gene	Chromosome	Other associated cancers
HBOC	*BRCA1*	17q21	Ovary, fallopian tube, male breast, pancreas, possibly cervix and uterus
HBOC	*BRCA2*	13q12-13	Ovary, fallopian tube, male breast, pancreas, prostate, possibly biliary tract, stomach, and melanoma
Li-Fraumeni	*p53*	17p13.1	Soft tissue and bone sarcomas, leukemia, brain, adrenocortical malignancies
Cowden	*PTEN*	10q22-23	Hamartomas, uterus, non-medullary thyroid
Hereditary diffuse gastric cancer syndrome	*CDH1*	16q22.1	Lobular breast cancer, diffuse gastric cancer
Peutz-Jeghers	*STK11*	19p13.3	Hamartomatous gastrointestinal tract polyps, small bowel, stomach, colorectal, pancreas, lung, uterus, ovary

Genetic counseling process

Patients affected by BC or unaffected individuals (probands) who may be at increased risk for the disease should be referred for genetic assessment. Genetic counseling is a multi-step communication process dealing with complex and often highly charged information which should be non-directive: the aim is to identify and counsel individuals at different risk of developing cancer, distinguishing between those at true high risk (highly penetrant HBOC), those at modestly increased risk (multifactorial etiology or low penetrance alleles), and those at average risk. Genetic testing is therefore just one part of this process and should only be offered in the context of a comprehensive program of pre- and post-test counseling, by professionals with appropriate knowledge and experience in the field.[26] Typically, genetic counseling includes a risk assessment/pre-test visit, which for many individuals ends up without any test indication, and a subsequent test/post-test visit for the proportion of high-risk subjects for whom a test indication exists. In this second population, counselees should be given enough time to consider testing.

During the risk assessment/pre-test visit the subject undergoes genetic risk assessment, the indication and potential impacts of test results are discussed and informed consent for possible future testing is provided. The subject's motivations, expectations, current understanding of cancer genetics risk and testing process are addressed as well as the transmissible cancer risk to relatives.

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