

Hereditary breast cancer: review and current approach

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ABSTRACT

Hereditary breast cancer is a complex and important condition, representing about 10% of all breast cancer cases. Identifying high-risk patients and possible carriers of pathogenic genetic variants with indication for genetic testing is an essential step to care for these patients and their families. Treatment can be influenced, both surgical and adjuvant, by the existence of mutation, providing the possibility of better results and preventive measures. In Brazil, access to oncogeneticists and genetic counseling is limited. Mastologists and their teams must be trained to identify and conduct the approach of these patients, with the objective of offering an adequate and preventive care, as well as early diagnostics. In the present study, a literature review of hereditary breast cancer aspects, diagnostic, and implications, in patients with and without breast cancer, was performed, aiming to assist in the proper management offered by mastologists, considering general and Brazilian characteristics.

KEYWORDS: breast cancer; genetic testing; heredity; mutation; genetic predisposition.

INTRODUCTION

Breast cancer (BC) is the most common cancer type affecting women worldwide. In Brazil, the National Cancer Institute (INCA) estimates more than 66,200 new cases for the triennial 2020–2022, corresponding to about 30% of all female cancers.¹

BC is known to be a heterogeneous disease, with different forms of presentation. Roughly 70% of all cases of BC are classified as sporadic, 20% as familial BC, and 10% as hereditary BC. Most of hereditary breast cancer (HBC) are due to variants in high penetrance genes, with early onset in premenopausal women and with an autosomal dominant heritage pattern. Familial BC has some similar aspects, but it often does not exhibit the dominant autosomal inheritance and the early appearance like in hereditary cases. In HBC, the individual is already born with one of the alleles containing a pathogenic variant, inherited from the father or mother, present in each cell of the body, leading to a greater predisposition to cancer. Most of the breast cancer susceptibility genes are suppressor genes, and there is germline mutation in high or moderate penetrance genes, with a 50% risk of transmitting the genetic alteration to the offspring.

Studies in molecular genetics demonstrate that cancer is a genetic illness due to inherited or acquired DNA mutations, which lead to oncogenes activation and/or suppressor genes inactivation². As mentioned, most BC predisposing genes are tumor suppressor genes, involved in DNA damage repair pathways and cell cycle control: BRCA1, BRCA2, TP53, PTEN, STK11, CDH1, CHEK2, ATM,

BRIP1, and PALB2. Mutations that occur in these genes are loss of function, and cause genomic instability and uncontrolled cell cycle, leading to uncontrolled proliferation of tumor cells³.

Carriers of genetic variants of susceptibility to BC are at increased risk of breast cancer and other tumors, both malignant and/or benign, and need to be identified, because this diagnosis has personal and family implications. In addition, HBC is frequently associated to unfavorable prognostic factors, especially in BRCA1-related carcinomas, such as high histological grade, angiolymphatic invasion, presence of basal cytokeratins and negative hormone receptors, which indicate a higher frequency of triple negative tumors when compared to sporadic carcinomas (60%–80% versus 15%–20%)⁴.

Original Knudson model is the most widely accepted for explaining many familial cancers, including breast cancer. With this model, the individual is already born with a genetic variant, and the second event (or second hit) occurs throughout life, usually at a younger age, which may be a mutation in the DNA or another mechanism of gene silencing. In hereditary cancers, the most common is a DNA mutation in the second allele, which may be a pontual mutation or an extensive deletion in the normal allele⁵.

Many aspects of HBC are still unknown. Even after the identification of moderate penetrance genes, a significantly number of patients with high family history for BC have no genetic variant known. Low penetrance genes have also been identified and have uncertain role in the scenario of HBC. Moreover, the same germline genetic mutation can present different forms of presentation

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(for example, age of onset and tumor characteristics), showing the presence of risk-modifying factors, capable of affecting the penetrancy and the expressiveness of the high-risk genetic variants.

Consequences of diagnosing a genetic mutation of risk for breast cancer should always be discussed before and after testing, involving, whenever possible, a multidisciplinary evaluation and a genetic counseling. Offering genetic counseling is still a complex issue in Brazil because oncogenetics are scarce and concentrated in large cities.

METHODS

Literature review was conducted by data base from PubMed, Scientific Electronic Library Online (SciELO), and Medical Literature Analysis, and Retrieval System Online (MEDLINE). The search was carried out during April and May 2020, using the terms breast cancer, hereditary breast cancer, genetic testing, hereditary predisposition, BRCA mutation. Articles were selected by their title, year of publication, and scientific evidence. The search was limited to articles published in English. A total of 87 articles were preselected by their abstract or full text, and 64 articles were used to build the present study.

RESULTS

Identifying high-risk patients for breast cancer

Identifying high risk patients for BC is an important step in the medical practice. The definition of high risk includes women with a lifetime risk of developing the disease greater than 20%, or a relative risk greater than four or five^{6,7}. There are four situations that encompass this definition:

- personal history of atypical ductal hyperplasia or lobular neoplasia (atypical lobular hiperplasia and lobular carcinoma *in situ*);
- irradiation of the chest wall at a young age;
- strong family history without the presence of a genetic variant linked to hereditary cancer;
- carriers of genetic variants linked to hereditary cancer.

Risk measurement can be assessed with clinical history, heredogram, risk prediction models, and genetic testing. BC risk calculation models mostly used in clinical practice and available on the internet are: Tyrer-Cuzick (IBIS Breast Cancer Risk Evaluation Tool; available on <https://www.ems-trials.org/riskevaluator/>), BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Cancer Estimation Algorithm; available on <https://www.ccge.medschl.com.ac.uk>), BRCAPRO (available on <https://www4.utsouthwestern.edu/breasthealth/cagene>) and PENN II (available on <https://pennmodel2.pmacs.upenn.edu/penn2/>)⁸⁻¹⁰. Appropriate personal and family history are essential for guidance on the possibility of hereditary disease. Not every high-risk patient has characteristics of hereditary breast

cancer. Then, assistant professionals must know how to identify high-risk patients to adopt the appropriate management and direct which patients at risk would have an indication for genetic testing.

Another way frequently used to identify a candidate for genetic testing is based on the guidelines of important scientific institutions or societies. Tables 1 and 2 show the National

Table 1. National Comprehensive Cancer Network (NCCN) criteria for genetic testing (modified for specific genes and hereditary cancer syndromes) – version 5.2020.

NCCN 2020 – Genetic testing criteria		
Personal history of breast cancer	Age ≤ 45	All patients
	Age 46–50	Unknown family history A second breast cancer at any age
		≥ 1 close relative with breast or ovarian cancer at any age
	Age ≤ 60	Triple negative breast cancer
	Any age	Male breast cancer
		≥ 1 relative with breast cancer with: <ul style="list-style-type: none"> • Breast cancer ≤ 50 years old • Ovarian cancer • Male breast cancer • Prostate cancer Gleason ≥ 7 • Pancreatic cancer
≥ 3 total diagnoses of breast cancer in patient and/or close relatives		
Personal history of others neoplasias	Any age	Ashkenazi Jewish ancestry
		Epithelial ovarian cancer
		Metastatic prostate cancer Gleason ≥ 7
		Pancreatic cancer
Family history of breast cancer		Ashkenazi Jewish ancestry
		Family with known pathogenic or likely pathogenic variant
Personal history or Family history with 3 or more members		1 st or 2 nd degree relatives with testing criteria
		Breast cancer, sarcoma, central nervous system tumor and leukemia (TP53)
		Colon, endometrial, thyroid, and kidney cancer, signs of Cowden syndrome (PTEN)
		Lobular breast cancer and gastric cancer (CDH1)
Regardless of family history of breast cancer	Any age	Breast, gastrointestinal, pancreatic, and sexual cord cancer, signs of Peutz-Jeghers syndrome (STK11)
		Test with alteration considered eligible for target therapy
		Pathogenic or likely pathogenic variants of BRCA 1 or 2, detected in tumor genetic profile

Table 2. Brazilian Supplementary Health National Agency (*Agência Nacional de Saúde Suplementar* - ANS) criteria for genetic testing, 2018.

Hereditary breast and ovarian cancer - GENES BRCA1 and BRCA2 National Supplementary Health Agency		
Coverage	Criteria	
1. Mandatory coverage for women with a current or previous diagnosis of breast cancer when at least one of the following criteria is met:	a. Diagnosis of breast cancer at age ≤ 35 ;	-
	b. Diagnosis of breast cancer aged ≤ 50 , and one of the following criteria:	I. a second primary breast tumor (*); II. \geq one family member of 1 st , 2 nd and 3 rd degrees with breast and/or ovarian cancer;
	c. Diagnosis of breast cancer aged ≤ 60 if triple negative breast cancer (estrogen receptor (ER), progesterone receptor (RP) and HER2 receptor negative);	-
	d. Diagnosis of breast cancer at any age plus one of the following:	I. \geq one family member of 1 st , 2 nd , and 3 rd degrees with female breast cancer aged ≤ 50 ; II. \geq one family member of 1 st , 2 nd , and 3 rd degrees with male breast cancer at any age; III. \geq one family member of 1 st , 2 nd , and 3 rd degrees with ovarian cancer at any age; IV. \geq two relatives of 1 st , 2 nd , and 3 rd degrees on the same side of the family with breast cancer at any age; V. ≥ 2 relatives of 1 st , 2 nd , and 3 rd degrees on the same side of the family with pancreatic or prostate cancer (Gleason score > 7) at any age. (* (*) In the case of bilateral breast cancer or two primary neoplasms in the same breast (confirmed by anatomopathological reports), each of the tumors must be considered independently.
2. Mandatory coverage for women with a current or previous diagnosis of ovarian cancer (epithelial tumor) at any age and regardless of family history.	-	-
3. Mandatory coverage for men with a current or previous diagnosis of breast cancer at any age and regardless of family history.	-	-
4. Mandatory coverage for patients with pancreatic cancer and \geq two relatives of 1 st , 2 nd , and 3 rd degrees on the same side of the family with breast and/or ovarian and/or pancreatic or prostate cancer (Gleason score ≥ 7) at any age.	-	-
5. Mandatory coverage for patients with prostate cancer (Gleason score ≥ 7) and \geq two relatives of 1 st , 2 nd , and 3 rd degrees on the same side of the family with breast and/or ovarian and/or pancreatic or prostate cancer (score of Gleason ≥ 7) at any age.	-	-
6. Mandatory coverage for testing the t founding Ashkenazi mutations in the BRCA1 and BRCA2 genes in patients of Ashkenazi Jewish origin when at least one of the following criteria is met:	a. breast cancer at any age and regardless of family history; b. ovarian cancer at any age and regardless of family history; c. pancreatic cancer at any age with \geq one family member of the 1 st , 2 nd , and 3 rd degrees with breast, ovarian, pancreatic or prostate cancer (Gleason score ≥ 7).	-

Continue...

Table 2. Continuation.

Hereditary breast and ovarian cancer - GENES BRCA1 and BRCA2 National Supplementary Health Agency		
Coverage	Criteria	
7. Mandatory coverage for patients over 18 years old, diagnosed or not with cancer, regardless of gender, when there is a deleterious mutation in BRCA1 or BRCA2 in a family member of 1 st , 2 nd , and 3 rd degrees.	-	-
8. Mandatory coverage for individuals with isolated breast cancer, who have a limited family structure. Limited family structure is the absence, in at least one of the branches (maternal or paternal) of the family, of at least two women from the 1 st , 2 nd , or 3 rd grades who have lived beyond 45 years of age at the time of the assessment. This description includes individuals who are unaware of their biological family data.	-	-
9. Mandatory coverage for individuals with breast cancer, but with limited family structure (absence of two female of 1 st , 2 nd , or 3 rd degree relatives in one of the strains - maternal or paternal - who has lived beyond 45 years of age). Analysis method used in a staggered way:	<p>1. In cases in which the genetic mutation has already been identified in the family, perform only the search for the specific mutation. For patients of Ashkenazi Jewish origin in which the family mutation is a founding mutation, it is justified to carry out the analysis of the three Ashkenazi founding mutations instead of analyzing only the family mutation, because of the possibility of more than one mutation in BRCA genes in Ashkenazi families. If the family is of Ashkenazi Jewish origin and the family mutation is not one of the three founding mutations, it is still justified to test these three mutations in addition to the mutation that is known to secrete into the family;</p> <p>2. In the cases of patients listed in items 1, 2, 3, 4, 5, 6, and 8, perform the New Generation Sequencing exam for the entire coding region of BRCA1 and BRCA2, and MLPA of BRCA1 and BRCA2;</p> <p>3. In the case of patients included in item 6, perform the test of the three Ashkenazi founding mutations in the BRCA1 and BRCA2 genes, namely: BRCA1 185delAG (c.66_67delAG, p.Glu23fs), BRCA1 5382insC (c.5263insC, p.Gln1756fs), and BRCA2 6174delT (c.5946delT, p.Ser1982fs). If none of these mutations are identified and other eligibility criteria are met as described in items 1, 2, 3, 4, 5, 7, and 8, the analysis should be performed following the step analysis criteria described for each item.</p>	

Comprehensive Cancer Network (NCCN) and the Brazilian National Supplementary Health Agency (*Agência Nacional de Saúde - ANS*) criteria for genetic testing, respectively.

Recently, the American Society of Breast Surgeons (ASBS) reviewed its consensus guidelines and recommended that genetic

testing should be available to all patients with a personal history of BC. Recommendations were based on identification of pathogenic genetic variants as influencing patient management in terms of high-risk screening and risk-reduction approach, as well as specific therapeutics options related to surgery,

radiotherapy, and systemic treatment¹¹. Moreover, Beitsch et al., in a multicenter prospective registry study with 959 patients, concluded that approximately 45% of patients with BC with clinically actionable germline variants are left out when testing is restricted to patients meeting current NCCN guidelines and when testing strategies are limited to panels containing only BRCA1/2¹².

Genetic tests for hereditary predisposition to cancer

Genetic tests to identify BC susceptibility genes are indicated when there is clinical suspicion, usually after heredrogram, risk prediction models, or specific guidelines. Before testing, patients need to be made aware of the implications that test results can have (pre-test counseling). When results become available, patients should be reminded of these implications and be provided the appropriate clinical context for the results to make informed decisions (post-test counseling). All genetic testing should be performed in the setting of informed consent. Knowing that not all carriers of pathogenic genetic variants will develop BC is also important. On the other hand, a negative test result does not necessarily imply the absence of risks.

In general, when family history is suggestive, the best scenario is to test the individual with a cancer diagnosis, because this increases the probability of a positive result. For multiple affected individuals, the preference is to start testing the youngest individual.

Genetic testing for germline variants can be done with a blood sample (analyzing leukocyte DNA samples) or an oral mucosa/saliva sample (analyzing epithelial cells).

In practice, three main types of tests are used: the first generation of genetic sequencing using the Sanger technique was considered the gold standard for research pontual mutations for a long time. It is an accurate, but laborious and expensive method, that needs large amounts of DNA and examines individual fragments of the gene of interest to a single patient at a time¹³. Its limitation is not detecting large rearrangements in DNA. Secondary analysis found that 6%–18% of individuals who are BRCA mutation negative by this technique can be explained by large insertions and deletions in the BRCA1 and BRCA2 genes, detected using other new technology¹⁴. Currently, its use is restricted to situations in which a certain mutation in the family is already known and has the desire to research it. The Next Generation Sequency (NGS) technique can analyze multiple genes simultaneously, which optimizes costs and is the current preference. However, it has a low sensitivity for large insertions/deletions and can found an expressive finding of variants of uncertain significance (VUS)^{15,16}. These multigenic panels can encompass high and moderate penetration genes. NGS has been recently updated to detect copy numbers alterations (CNA), with highly confident detection rates. Another technique is the Multiplex Ligation-dependent

Probe Amplification (MLPA), a multiplex PCR method developed to detect abnormal copy numbers of different genomic DNA sequences, not rarely used to complement diagnostic research and identify major deletions, especially in BRCA1, BRCA2, and TP53 genes. Most of the pathogenic genetic variants in the BRCA genes are punctual and detected by the Sanger technique or NGS multigenic panels, but data show up to 12% of changes in these genes are due to deletions detected by MLPA¹⁷.

Currently, most genetic studies are carried out by multigenic panels with NGS platforms, complemented, when needed, by the MLPA technique, mainly in cases of strong family suspicion and negative panel results.

The possible results of a genetic test are:

- class 1: benign variant;
- class 2: likely benign variant;
- class 3: variant of uncertain significance (VUS);
- class 4: likely pathogenic variant;
- class 5: pathogenic variant.

Table 3 shows the genetic testing results and interpretation. VUS should always be reported and periodically reassessed. Most VUS will be reclassified into benign or likely benign categories.

Hereditary breast cancer susceptibility genes

Genetic biomarkers of cancer risk can be categorized into two primary criteria: penetrance and population frequency. Penetrance refers to the estimate that a specific condition, in this case cancer, will occur in the presence of a specific genotype. It refers to the probability, in percentage, to express typical phenotypes at specific timepoints.

The Human Genome Variation Society (HGVS) developed an internationally accepted nomenclature that recommends the use of the neutral term variant rather than mutation. Risk variants mostly show an inversely proportional impact, from very rare ones, with high penetrance, to the common low-risk single nucleotide variants, with high allele frequency (of up to 50%):

Table 3. Results and interpretation of genetic testing for cancer predisposition.

Result	Interpretation
True positive	Carrier of a cancer predisposition variant that is already known and present in the family.
True negative	Individual does not carry a known cancer predisposing gene that has been identified in another family member.
Indeterminate	Individual does not carry a known gene for cancer predisposition and the status of another family member is unknown.
Inconclusive (VUS)	Carrier of a mutation in a gene that currently has unknown clinical significance.

VUS: variants of uncertain significance.

- High-risk variants: very rare in the population with a minor allele frequency < 0.005. The conferred relative risk of breast cancer is higher than 4;
- Moderate-risk variants: rare, with a minor allele frequency of 0.005–0.01. Pathogenic variants confer a relative risk of 2–4;
- Low-risk variants: minor allele frequency > 0.01, and conferred risk of breast cancer of less than 1.5-time¹⁸.

The number of cases in which BC resulted from genetic polymorphisms and genes with low-penetrance (regarding environmental interactions) is considerably larger than the number of BC cases resulted from mutations of high penetrance genes. In the HBC scenario, most cases are due to BRCA1 and BRCA2 variants, whereas others genes are responsible for about 40% of all cases (Figure 1).

High-penetrance genes

BRCA1 and BRCA2

The first major gene associated to HBC was the BRCA1, located on chromosome 17q21, and identified in 1990 with linkage analysis in families with suggestive pedigrees¹⁹. In 1994, BRCA2 gene, located on chromosome 13q12-13, was also identified. They have an autosomal dominant inheritance pattern.

BRCA1 and BRCA2 (BRCA1/2) mutations confer a very high life-time risk of BC in the range of 50%–85% for BRCA1, and up to 45% for BRCA2²⁰. The risk of ovarian cancer (OC) is also higher: 30%–60% for BRCA1, and 10%–25% for BRCA2 carriers²¹. A greater incidence of other cancers is documented such as prostate, pancreatic, fallopian tube, and primary peritoneal adenocarcinoma for both BRCA1/2 genes, and male BC and melanoma for BRCA2 gene.

Most BRCA1-related breast cancers have a basal-like phenotype and they are also characterized by the lack of expression of estrogen-receptors, progesterone-receptors, and of no over-expression of human epidermal growth factor 2 (triple negative BC). In addition, over-expression of the epidermal growth

fator receptor (EGFR) has been associated to BRCA1-related breast cancers²². The immunophenotype and gene expression profile of BRCA2-related cancers are very similar to sporadic breast cancers, with a predominance of positive hormone receptor tumors (luminal BC). Both BRCA1 and BRCA2 tumors exhibit a higher histological grade; BRCA1 tumors are more often poorly differentiated (Grade 3), whereas BRCA2 tumors more frequently are moderately or poorly differentiated (Grades 2 and 3)²³. The majority of BRCA1 and BRCA2-associated ovarian cancers are classified as high-grade serous carcinomas.

In terms of surveillance, an annual breast nuclear magnetic resonance (MRI) in conjunction with annual mammography screening in BRCA1 and BRCA2 carriers from the age of 30 years is more sensitive than annual mammography alone, detecting BC at an earlier stage^{24–26}. Moreover, lifestyle changes and risk reduction strategies should be discussed. Trials involving chemoprevention with Tamoxifen 20 mg once a day for five years have demonstrated that BC risk can be reduced by 40%–50% in women at high risk, although not necessarily in pathogenic variant carriers²⁷. Whereas BRCA1 BC are predominantly estrogen receptor (ER) negative and BRCA2 BC are predominantly ER positive, and considering that data are limited regarding the benefit of Tamoxifen in BRCA carriers, Tamoxifen use may be an option for patients who do not want to undergo risk-reducing surgery^{28,29}. Risk-reducing bilateral mastectomy should be discussed, and literature shows more than 90% reduction in the BC incidence³⁰. A recent study showed that bilateral risk-reducing mastectomy in mutation carriers had an impact on mortality in BRCA1 carriers, although the impact in BRCA2 carriers was less evident³¹. Nipple-sparing mastectomy is a safe and appropriate technique to be evaluated, according to breast size, tumor localization, and degree of ptosis. In addition, prophylactic salpingo-oophorectomy (PSO) confers a 72%–88% risk reduction in OC and fallopian tubal cancer. Literature data show PSO confers a reduction in OC-specific and all-cause mortality in BRCA carriers^{31–33}. Therefore, PSO is recommended for BRCA carriers who have completed childbearing, and it should be performed by age 35–40 in BRCA1 carriers, and by age 40–45 in BRCA2 carriers³¹. Early surgical castration causes early menopause and increases the risk of cardiovascular disease and osteoporosis. On the basis of available data from observational studies, hormone replacement therapy after PSO should not be performed in patients affected by BC, but it has not shown an increased risk of BC among cancer-free BRCA carriers who have undergone risk-reduction bilateral mastectomy³⁴.

After a BC diagnosis, surgical approach must be individualized and well debated with patients. According to the recent guidelines by the American Society of Clinical Oncology (ASCO), American Society for Radiation Oncology (ASTRO), and Society of Surgical Oncology (SSO) both breast conservative therapy (BCT) and mastectomy are possible³⁵. Observational studies suggest

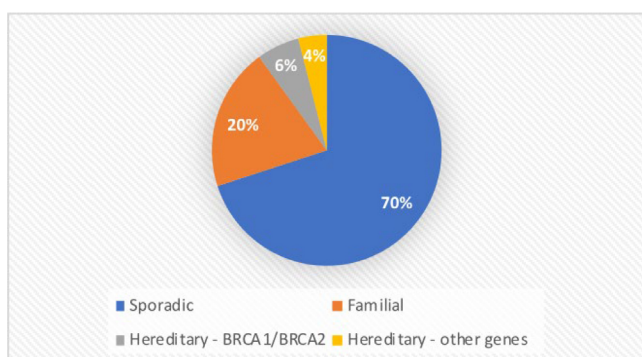


Figure 1. Breast cancer classification by cause.

BCT is a safe surgical option for managing BC in BRCA carriers. However, BRCA 1/2 carriers should be informed about the risk of contralateral breast cancer (CBC) and a possible increased risk of a new primary cancer in the ipsilateral breast when compared to noncarriers. Cumulative CBC risk 20 years after a first primary BC is 40% for BRCA1 and 26% for BRCA2 carriers. Current evidence suggests that contralateral risk-reducing mastectomy is effective for BRCA1 carriers, reducing mortality^{32,36}. The benefit of contralateral prophylactic mastectomy depends, however, on the previous or current tumor prognosis, age of patient and clinical conditions for the procedure. Recently, van den Broek et al, when comparing BCT *versus* mastectomy in BRCA mutation carriers to noncarriers, found low local recurrence rates, similar overall survival, and no difference in local recurrence rate³⁷.

Radiotherapy-related toxicity in patients with breast cancer with BRCA1/2 variants showed that rates of radiation-associated complications in women with BRCA1/2 variants were comparable to rates observed in women with sporadic breast cancer^{38,39}.

Two phase III trials (OlympiAD and EMBRACA) randomly assigned patients after chemotherapy in HER2-negative, BRCA-associated metastatic BC, and showed longer progression-free survival with PolyADP-Ribose Polymerases (PARP) inhibitor^{40,41}. The Food and Drug Administration has approved 2 PARP inhibitors (Olaparib and Talazoparib) for germline BRCA-associated metastatic BC. In Brazil, Olaparib was approved in this setting by the Brazilian Health Regulatory Agency (*Agência Nacional de Vigilância Sanitária* - ANVISA) in 2018⁴².

TP53

One of the most studied tumor suppressor gene is the tumor protein 53 (TP53), located on chromosome 17p13.1. Inherited TP53 mutations are associated to the rare autosomal dominant disorder, the Li Fraumeni Syndrome (LFS). Female variant carriers have a nearly 100% lifetime risk of cancer compared to 73% for males, difference which is caused by BC⁴³. Unlike other high-risk genes that mostly display risk associated to truncating mutations, genotype–phenotype analysis in LFS families has revealed that germline missense mutations are more frequent. Other than breast cancer in women, TP53 variant carriers are at increased risk of early-onset and multiple primary cancers, including sarcomas, brain, and adrenocortical tumors. Lymphoma, leukemia, melanoma, lung, pancreatic, prostate, and ovarian cancers also seem to be more frequent. Childhood-onset tumors exist, and the most common are brain tumors, followed by sarcomas^{44,45}.

In Brazil, because of the founder variant present in a significant part of the population, especially in the Southern region, appropriate investigation and management are therefore important. Recently, a TP53 mutation called p.R337H is drawing the attention of professionals who deal with breast cancer, as it has been identified in a significant portion of patients⁴⁶.

Carriers of a TP53 pathogenic variant should receive intensive surveillance. Breast MRI should be offered annually from age 20, as well as mammography after age 30. Risk-reducing bilateral mastectomy in patients without BC and contralateral risk-reducing mastectomy in patients with BC should be suggested⁴³.

TP53 gene may be the most critical tumor suppressor gene in preventing the development of cancer. It plays an important role in cell cycle control and apoptosis, and provides the cell with the ability to respond to and repair DNA damage after cellular stress by triggering multiple downstream repair pathways. Thus, carriers of a TP53 variant would be expected to be unable to repair tissue damage from DNA-damaging RT and be at risk for significant RT-associated sequelae. For these reasons, there is limited evidence to inform the clinical question of the role of RT in women who carry a TP53 mutation. Outcomes reported in published case reports support this recommendation against RT in women with breast cancer who carry a TP53 variant^{47,48}. Thus, mastectomy is the recommended therapeutic option.

Based on Toronto protocol, whole-body MRI and brain MRI should be performed at the first preventive clinical screening evaluation in TP53 carriers of pathogenic germline variants, because of the high risk of sarcomas and central nervous system, adrenocortical, and other tumors⁴⁹. However, due to the Brazilian social and economic reality, and the limited assess of most citizens to these technologies, feasibility of this recommendation is hard to be adopted.

PTEN

Cowden syndrome is a rare condition caused by germline mutations in tumor suppressor gene PTEN, located on chromosome 10q23.31. Studies of carriers of disease-causing variants show a considerably high lifetime risk of breast cancer, with low age of onset. Carriers are also at an increased risk of several other malignancies, especially thyroid and endometrial cancer. The syndrome is otherwise characterized by multiple hamartomas of the gastrointestinal tract, macrocephaly, and benign tumors, such as lipomas⁵⁰.

Surveillance with clinical breast examination since age 25, and annual MRI and mammography starting between 30 and 35 years of age is recommended. Risk-reducing mastectomy is controversial, but it can be considered due to the risk of up to 85% by the age of 75 in women⁵¹.

CDH1

The CDH1 gene, located on chromosome 16q22.1, encodes a protein responsible for cell-to-cell adhesion and functions as a cell invasion suppressor⁵². E-cadherin germline mutations are responsible for hereditary diffuse gastric cancer (HDGC). Carriers of truncating variants are at a very high risk of diffuse

gastric carcinoma at young age and, in addition, an estimated relative risk of breast cancer of 6.6 (predominantly lobular breast cancer)⁵³. Recent studies have provided evidence of lobular breast cancer as the first manifestation of HDGC. Deleterious CDH1 mutations have been identified in women with bilateral lobular breast cancer without a family history of diffuse gastric cancer. The risk of colorectal cancer also appears to be increased⁵⁴.

MRI screening, in women with or without mammography, started at 30 years of age, is the current recommendation for CDH1 mutation carriers. Although evidence is limited, prophylactic mastectomy can be discussed, especially when a family history of BC is present⁵⁵.

Prophylactic partial gastrectomy can be indicated as a preventive measure, given that the risk of gastric cancer reaches 67% in men and 83% in women⁵⁶.

STK11

The tumor suppressor STK11, located on chromosome 19p13.3, is another gene with a gene product important for cell cycle regulation and mediation of apoptosis. Deleterious mutations cause Peutz–Jeghers Syndrome, characterized by intestinal hamartomatous polyps and mucocutaneous pigmentation. In addition, the lifetime risk of breast cancer by 60 years old is 32%–54%⁵⁷. Other associated tumors with markedly elevated risk are cancers of gastrointestinal origin and pancreatic cancer. Female carriers are also at an increased risk of ovarian sex cord-stromal tumors and a rare tumor of the cervix, the adenoma malignum. Carriers of STK11 mutations have a cumulative lifetime risk of any cancer of up to 85%⁵⁷.

Breast clinical examination associated to MRI and mammography from the age 25 is recommended⁵⁸. Prophylactic mastectomy, oophorectomy, and hysterectomy are controversial procedures, but they can be discussed individually⁵⁹.

Moderate penetrance genes

Studies have identified several additional DNA repair genes that interact with BRCA genes and confer an approximate two-fold increase in BC risk, including CHEK2, ATM, and PALB2⁶⁰. NBN and NF1 genes are also genes of moderate penetration with increased risk of breast cancer⁶¹. Recently, BARD1, RAD51D, and MSH6 were identified as moderate-penetrance genes.

The lifetime risk of BC associated to a variant in PALB2 is approximately from 35% to 60%, whereas with ATM and truncating CHEK2 mutations lifetime risk is from 25% to 30%⁶². In a meta-analysis, loss-of-function PALB2 variants have yielded a combined estimated relative risk for BC of 5.3 in carriers of pathogenic mutations, which suggests that PALB2 should, instead, be possibly placed in the high-risk category⁶³.

According to the recent guidelines by ASCO, ASTRO, and SSO moderate genes mutation carriers should undergo high-risk breast

screening with annual MRI and mammogram. Mutation status alone should not determine local therapy decisions, and BCT should be offered when it is an appropriate option. Evidence regarding contralateral BC is limited. Contralateral prophylactic mastectomy decision should not be based predominantly on mutation status³⁵.

DISCUSSION

The identification of high-risk patients for BC is crucial for the current clinical management. Likewise, suspecting patients liable to carry a hereditary genetic mutation at risk for BC and other neoplasms has become an important measure in health-care, with personal and family impacts. Considering that roughly 10% of BC cases are hereditary, one in 10 cases have an inherited genetic component to be detected. Worldwide, there is a sub-identification of cancer susceptibility mutations. Population-based approaches to genomic screening remain costly and involve challenges in high through-put sequencing, obtaining informed consent, correct interpretation of genomic variants, and post-test implications⁶⁴.

In Brazil, the limitation of access to oncogeneticists and genetic tests is a real issue and clearly needs improvement. There is an evident gap in this assessment, especially in the public health system, but also in supplementary health. Access to genetic test must involve a multidisciplinary team, with pre and post-test counseling and individual discussion case-by-case, both in the positive and negative scenario for genetic mutation. HBC approach involves integration between indication, application, and understanding of germline testing. For this, based on the ASBS recommendations on its last consensus guidelines, the training and betterment of mastologist doctors should be encouraged¹¹. Cancer genetics knowledge allows mastologists to initiate and guide genetic testing for their patients. Strategies related to public awareness, education, integrated services, telemedicine, and multidisciplinary approach are needed.

An appropriate screening strategy and the discussion of risk-reducing measures must be offered. Any patient found to have a hereditary predisposition for BC should be informed of all options to reduce their risk: lifestyle changes, chemoprevention, and risk-reducing surgeries.

The recent guidelines by ASCO, ASTRO, and SSO brought an updated guide for both HBC driving and management. According to it, evidence support prophylactic mastectomy for BRCA1, BRCA2, and TP53 mutation carriers³⁵. For the other high penetration genes, evidence is poor, with no clear basis for prophylactic surgery, as well as for moderate penetrance genes³⁵. Surgical management of BC in a pathologic variant carrier must consider age, clinical condition, staging at diagnosis and can include both BCT and mastectomy with oncological safe. However, the risk of a new primary tumor

in the breast treated with conservative surgery appears to be greater. Contralateral mastectomy is an option, especially for the therapeutic mastectomy candidates, and should be considered according to the prognostic associated to the primary cancer. Likewise, RT is safe and an important adjuvant treatment, except in those with TP53 variant, in which the risk of radio-induced tumors is high³⁵. Finally, in the systemic treatment, evidence suggest that for germline BRCA1/2 mutation carrier with metastatic BC, platinum chemotherapy is preferred rather than taxane therapy for patients who have not previously received platinum. There are no data to address platinum efficacy in other germline mutation carriers³⁵. For BRCA1/2 mutation carriers with metastatic HER2-negative BC, Olaparib or Talazoparib (oral drugs) should be offered as an alternative to chemotherapy in the first- to third-line settings. In Brazil, Olaparib is approved by ANVISA since 2018. For BRCA1/2 mutation carriers with metastatic HER2-negative

BC, there are no data directly comparing efficacy of PARP inhibitors to platinum chemotherapy³⁵.

CONCLUSIONS

HBC is still a complex disease, with a wide field of approach to be explored, from the suspicion and identification of individuals and families with pathogenic variants, with the adoption of risk-reducing measures and specific therapies in those who develop cancer. Strategies to improve this identification must be developed, refined, and disseminated.

Mastologists and their multidisciplinary team must be trained in the approach of HBC to facilitate the access of carriers to educational and investigative processes.

The appropriate treatment after the diagnosis of an HBC can offer better results and be cost-effective in terms of disease control and preventive measures.

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