The Molecular Pathology of Hereditary Breast Cancer

J. Palaciosa M.J. Robles-Fríasa M.A. Castilla a M.A. López-Garcíaa J. Benitezb

aPathology Department, HHUU Virgen del Rocío, Sevilla, and bHuman Genetics Programme, Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain

Key Words
Breast cancer, hereditary · BRCA · Genotype · Molecular features · Histopathological features · Therapeutic implications

Abstract
Hereditary breast cancer arising in carriers of mutations in the BRCA1 and BRCA2 genes differs from sporadic breast cancer and from non-BRCA1/2 familial breast carcinomas. Most BRCA1 carcinomas have the basal-like phenotype and are high-grade, highly proliferating, estrogen receptor-negative and HER2-negative breast carcinomas, characterized by the expression of basal markers such as basal keratins, P-cadherin and epidermal growth factor receptor. BRCA1 carcinomas frequently carry p53 mutations. The basal-like phenotype is only occasionally found in BRCA2 carcinomas, which tend to be estrogen and progesterone receptor positive. BRCA1 and BRCA2 loss of heterozygosity is found in almost all BRCA1 and BRCA2 carcinomas, respectively. Both genotypes have a low frequency of HER2 expression/amplification. In addition, comparative genomic hybridization and array expression studies have revealed differences in chromosomal gains and losses as well as expression patterns between genotypes. Several studies have shown that hereditary carcinomas that are not attributable to BRCA1/2 mutations are heterogeneous and have phenotypic similarities to BRCA2 tumors. A small group of cases are secondary to mutations in other breast cancer susceptibility genes, such as p53, PTEN or CDH1. As a result of the low frequency of breast carcinomas attributable to mutations in these genes, it is very difficult to establish a specific phenotype for each genotype, other than the association of lobular carcinomas with CDH1 germline mutations. The pathological and molecular features of hereditary breast cancer can drive specific treatments and influence the process of mutation screening.

Introduction

The existence of a strong hereditary predisposition to breast cancer has been recognized for more than a century. To date, up to 5–10% of all breast cancers are caused by germline mutations in well-identified breast cancer susceptibility genes. These genes have been divided into high-risk and low- to moderate-risk breast cancer susceptibility genes. The high-risk breast cancer susceptibility genes include BRCA1, BRCA2, PTEN, TP53, LKB1/STK11 and CDH1, with relative lifetime risks higher than 4 (but generally much higher at young ages). The CHEK2, TGFB1, CASP8 and ATM genes belong to the low- to moderate-risk breast cancer susceptibility genes. Germline mutations in BRCA1 and BRCA2 have been shown to account for approximately one third of hereditary breast cancers among young women with the disease. Mutations in other genes such as TP53, PTEN, STK11, CHEK2 and ATM account for a small proportion of hereditary...
breast cancer syndromes, often with distinct clinical features. However, in many breast cancer families, no predisposing gene mutation can be identified (in this article we will refer to them as non-BRCA1/2). Although the existence of other strongly predisposing genes is controversial, the search for additional breast cancer susceptibility genes remains an active area of investigation.

Heritable mutations in the mentioned genes, such as BRCA1 and BRCA2, lead to different further genetic alterations that are specifically involved in the development of each of these types of breast tumor. Knowing these molecular differences at the tumor level will allow us to meet central challenges in hereditary breast cancer management, such as defining tumor markers that can be used as predictors of the presence of the different germline alterations, or finding more specific drug targets. Unfortunately, only BRCA1- and BRCA2-related tumors have been more extensively analyzed from a morphological and molecular point of view and for this reason, in the present review, we will discuss in more detail the relevant data about the specific characteristics of BRCA1- and BRCA2-associated tumors regarding their pathology and molecular alterations.

Breast Carcinoma in BRCA1 and BRCA2 Mutation Carriers

Histopathological Features

Several studies during the last decade have demonstrated that cancer arising in carriers of BRCA1 and BRCA2 gene mutations differs morphologically from sporadic breast cancers of age-matched controls [1–4]. Invasive ductal carcinoma not otherwise specified is the most common histological subtype in hereditary and sporadic breast cancer, but there are subtypes more frequently associated with hereditary breast tumors. Thus, in the case of BRCA1 tumors, a higher incidence of medullary carcinoma (11%) has been reported than in BRCA2 mutation carriers (2%) and sporadic cases (1%) [5]. In addition, after excluding medullary carcinomas, BRCA1 tumors more frequently have a prominent lymphocytic infiltrate, foci of necrosis and pushing margins [2], which are some of the features that define the medullary histotype. To date, it is not clear whether or not some special histological types of invasive carcinomas are more frequent among BRCA2 mutation carriers. Although some authors have reported a higher incidence of tubular, lobular and pleomorphic lobular carcinomas, other studies have not confirmed these observations [1–2, 6].

Regarding tumor grade, BRCA1 tumors are more frequently poorly differentiated (grade 3) carcinomas. The proportion of grade 3 carcinomas ranged from 66 to 100% in different series [1, 4, 6–13], while the proportion of grade 3 tumors in age-matched sporadic tumors ranged from 15 to 55% [1, 5, 6, 8, 11]. BRCA2 tumors are more frequently moderately or poorly differentiated carcinomas (grades 2 and 3) [1, 6, 8, 10].

Ductal Carcinoma in situ

The frequency of ductal carcinoma in situ (DCIS) remains unclear in BRCA mutation carriers, and it is thought by some to be rare in BRCA1 patients [14]. The best data on the relative risk of DCIS in BRCA mutation carriers comes from the Breast Cancer Linkage Consortium [1]. This study showed that DCIS associated with invasive breast cancer was significantly underrepresented compared with the general population (41 vs. 56%, respectively). A follow-up study [2] also showed a marginally significant lower DCIS prevalence among BRCA mutation carriers.

Several other groups have reported the frequency of BRCA mutations in women with DCIS. Frank et al. [15] analyzed 10,000 individuals whose blood was tested for BRCA mutations. Twenty-six (13%) of 199 women with DCIS diagnosed before 50 years of age had deleterious BRCA mutations. This prevalence was significantly lower than BRCA mutation prevalence in women with invasive breast cancer before 50 years of age (587 of 2,466 patients; 24%) [15]. In the only population-based study that has examined family history and diagnosis of breast carcinoma in situ, Claus et al. [16] found a positive family history to be a significant risk factor for development of DCIS. In a subset of 369 women from the population sample, these authors found 11 BRCA mutations (3 BRCA1, 7 BRCA2, and 1 BRCA1 and BRCA2) for a prevalence of 3%, which is a BRCA mutation rate similar to that in invasive cancer in other populations.

To further clarify the role of DCIS in the development of BRCA-associated invasive breast cancer spectrum, Hwang et al. [14] have recently analyzed the frequency, histopathology and time to DCIS diagnoses in BRCA-positive patients compared with high familial risk, BRCA mutation-negative patients in a large cohort of women referred for genetic counseling. The authors found that among BRCA carriers, 37% had DCIS (with or without invasive cancer), compared with 34% in noncarriers. Univariate analysis showed that both DCIS and invasive cancer had an earlier onset in mutation carriers than in noncarriers. High-grade DCIS was more common in BRCA1 mutation carriers, while BRCA2 mutation carriers had a significantly lower prevalence of high-grade DCIS. A univariate analysis showed that 34% of BRCA1 carriers had high-grade DCIS compared to 15% of BRCA2 carriers. The prognostic value of DCIS stage was determined in a follow-up study [2] and it showed that the risk of invasive cancer was significantly higher in BRCA mutation carriers with high-grade DCIS than in carriers with low-grade DCIS.
carriers than in BRCA2 carriers and in patients without a mutation. In addition, no low-grade DCIS lesions were seen in BRCA1/2 mutation carriers, whereas 7% of DCIS in noncarriers with high familial risk were low grade.

**Immunohistochemical and Molecular Features
Hormone Receptors**

It is now well established that a high proportion of BRCA1 tumors are estrogen receptor (ER) and progesterone receptor (PR) negative [8, 10, 17–22]. Thus, the percentage of BRCA1-related breast cancers that are ER negative is between 73 and 90% in different series in contrast with 35% in controls [8, 10, 19]. In most series, these differences remain after adjusting for age and grade. Thus, the likelihood of ER negativity is 4.8 times higher in BRCA1 grade 3 tumors than in grade 3 sporadic cases [18]. Regarding PR expression, around 80% of BRCA1 tumors are negative for this receptor in contrast with only 41% of sporadic tumors [8, 10, 19]. On the other hand, tumors arising in BRCA2 mutation carriers do not differ from controls with regard to ER and PR expression. Thus, ER and PR expression has been reported in around 65% and 40–60% of BRCA2 tumors, respectively [17, 19–20].

**HER2**

HER2 protein overexpression subsequent to gene amplification, which occurs in 20–30% of sporadic breast cancers, has important prognostic and therapeutic implications. Thus, HER2-overexpressing tumors are candidates for first-line trastuzumab treatment and for the use of other HER2 inhibitors after trastuzumab resistance. Data on HER2 expression in BRCA1/2-associated tumors vary from series to series, probably as a consequence of differences in the techniques employed. HER2 expression (3+) is very infrequent in BRCA1 and BRCA2 carcinomas, with reported frequencies ranging from 0 to 3.7% [10, 17]. When also 2+ cases are selected, HER2 expression does not differ between BRCA and sporadic carcinomas [11]. With regard to HER2 amplification, few studies have used fluorescence in situ hybridization (FISH) to analyze gene status in BRCA carcinomas [10, 23–24]. One study reported that 19% of BRCA1 tumors had low levels of HER2 amplification (HER2:CEP17 ratio ≥ 2 to <3.1) [23], but failed to find high levels of HER2 amplification (HER2:CEP17 ratio >3.1) among BRCA1 carcinomas. Two other studies found no HER2 amplification among BRCA1 and BRCA2 carcinomas [10, 24]. A frequent chromosome 17 alteration in BRCA1 carcinomas is monosomy that has been reported in 35–61% of these tumors [10, 23]. This chromosomal abnormality may be significant, since chromosome 17 monosomy may be the second hit of inactivation in a proportion of BRCA1 tumors. BRCA2 tumors infrequently showed chromosome 17 monosomy, while around 20% were polysomic [10].

**p53**

Several studies have demonstrated a higher incidence of p53 immunostaining and p53 mutations in BRCA1 carcinomas relative to sporadic cases. Thus, these alterations have been observed in 37–77% of BRCA1-associated tumors [8, 10, 11, 17, 25–26], whereas they are only present in about 20% of sporadic controls. In addition, several observations suggest that BRCA1 mutations influence the type and distribution of p53 mutations seen in breast cancers. For example, comparison of the spectrum of p53 mutations in BRCA1 patients with those reported in the sporadic tumors reveals significant differences in distribution and base changes. Mutations at A:T base pairs were common in BRCA1-associated tumors. A number of these mutations have not been previously reported in human cancer databases, while others occur extremely rarely. Finally, changes were frequent at p53 codons that are not mutation hot spots and were located outside the p53 DNA-binding site [27]. The results of p53 studies in BRCA2 tumors are less conclusive than those in BRCA1 tumors. Some studies have found p53 overexpression in around 50% of BRCA2 carcinomas [17], whereas the percentage was lower than 20% in other series [10]. It has been reported that p53 mutations are present in 29% [28] to 63% [25] of BRCA2 tumors. However, p53 mutations were not found in BRCA2 tumors in 1 series [19].

**Proliferation, Cell Cycle and Apoptosis**

In contrast with sporadic tumors, BRCA1 tumors show a higher proliferative index evaluated by Ki-67 [10, 19] and in agreement with these findings, BRCA1 tumors overexpress proteins that promote cell cycle progression, such as cyclins E, A or B1 [29–31]. Another marker upregulated in these tumors is SKP2 [29, 31], the ubiquitin–protein ligase necessary for p27 ubiquitination. Interestingly, cyclin D1 expression is downregulated in BRCA1 tumors when compared with sporadic tumors, which can be explained by the fact that cyclin D1 is known to be upregulated by estrogen and progesterone [32]; on the other hand, BRCA1 tumors underexpress proteins related to the inhibition of the cyclin-CDK complexes, such as p16, p27 and p21 [29, 31]. In BRCA2 tumors, the expression of proteins related to cell cycle is similar to that observed in sporadic ER-positive tumors with respect to both cyclins promoting cell cycle progression (cyclins D, E, A and B1) and cyclin-
CDK complex inhibitors (p16, p27 and p21) [31], which are overexpressed compared with BRCA1 tumors. BRCA2 tumors frequently showed CCND1 amplification, an alteration that is absent in BRCA1 tumors [10].

Few studies have analyzed apoptosis markers in BRCA tumors. BAX and BCL2 expression together was of independent prognostic significance in other tumors as ovarian tumors. BAX and BCL2 expression frequently demonstrated higher caspase 3 activation was higher in high-grade, ER-negative tumors [35]. Expression studies using cDNA microarrays have also shown that BRCA1 mutation-positive tumors have increased expression of genes associated with inducing apoptosis (such as PDCD5) and decreased expression of genes involved in suppressing apoptosis (such as CTGF) [36].

DNA Repair Proteins
The main function of BRCA1 and BRCA2 genes is related to the response to DNA damage, and alterations in proteins involved in this cellular pathway have been demonstrated in BRCA1 and BRCA2 tumors. BRCA1 tumors overexpress CHEK2 and PCNA and underexpress RAD50 with respect to sporadic tumors, and do not show differences in the expression of other proteins such as RAD51, ATM or XRCC3 [37]. In BRCA2 tumors, CHEK2 protein overexpression has been observed as well. Interestingly, the nuclear expression of RAD51 in BRCA2 tumors is very low compared with BRCA1 and sporadic tumors, while cytoplasmic RAD51 staining is observed more frequently in BRCA2 tumors than in BRCA1 and sporadic tumors (50 vs. 15%). This may be explained by the fact that BRCA2 integrity is necessary to transport RAD51 to the nucleus, where it directs the reparation of double-strand breaks of the DNA by homologous recombination. It is important to note that this is one of the few markers that help to distinguish BRCA2-positive from sporadic tumors. Using the immunohistochemical expression of RAD51 and CHEK2, a BRCA2 tumor can be identified with a probability of 81% [37].

Chromosome Alterations
In addition to changes in HER2, several studies using FISH, loss of heterozygosity (LOH) analysis, comparative genomic hybridization (CGH) and CGH arrays have demonstrated several chromosome loci alterations in BRCA1 and BRCA2 tumors.

For example, a high proportion of low-level MYC amplification has been reported in 53% of BRCA1-mutated tumors compared to only 23% in sporadic tumors [38]. In another study, high-level MYC amplification was found in 18% of BRCA1 tumors. Chromosome 8 polysomy is also a frequent alteration in these tumors [10, 38]. FISH analysis has revealed amplification of MYB in around 30% of BRCA1 breast tumors, whereas this alteration is present in fewer than 5% of sporadic breast carcinomas [39]. These alterations are infrequent in BRCA2 tumors.

LOH and gene promoter methylation studies in BRCA1 and BRCA2 tumors from mutation carriers have demonstrated that LOH is the most common second hit of inactivation of these tumor suppressor genes. Thus, more than 90% of BRCA1 and BRCA2 carcinomas have LOH of the nonmutated allele [40–41]. In addition, LOH has been found in associated in situ lesions [19], nonneoplastic peritumoral tissues and even in other quadrants in the contralateral breast [42]. These findings suggest that these nonmalignant tissues already harbor significant amounts of the genetic alterations that may predispose to malignant transformation.

High-resolution CGH and CGH array studies have been used to explore chromosome alterations and to build a classifier that allows to differentiate BRCA1 and BRCA2 tumors [43–49]. These studies have shown that somatic genetic changes during tumor progression may follow different pathways in BRCA1 and BRCA2 mutation carriers. Although several genomic altered regions are common to the majority of breast cancers, hereditary tumors also show characteristic alterations that differentiate among them and from sporadic tumors. The genetic changes more commonly found in BRCA1 tumors are gains of 8q and 3q as well as losses of 4p, 4q and 5q. BRCA2 tumors present gains of 8q, 17q and 20q and lose 8p, 13q and 11q. In addition, ampicongs at 3q27.1–q27.3 in BRCA1 tumors and at 17q23.3–q24.2 and 20q13 in BRCA2 tumors [49] have been described. There are more differences between BRCA1 and controls than between BRCA2 and BRCA1 or between BRCA2 and controls [43].

Basal and Luminal Phenotypes in BRCA1 and BRCA2 Tumors
Gene expression studies using DNA microarrays have identified several distinct breast cancer subtypes [50], based on an intrinsic gene list that differentiates breast cancers into separate groups based only on gene expres-
sion patterns. These subtypes differ markedly in prognosis [51–53] and in the repertoire of therapeutic targets they express [54]. The intrinsic subtypes include 2 main subtypes of ER-negative tumors (basal-like and HER2 positive/ER negative) and at least 2 types of ER-positive tumors (luminal A and B) [51, 52]. Basal-like tumors typically show low expression of HER2 and ER and exhibit high expression of genes characteristic of the basal myoepithelial cell layer, including expression of cytokeratin 5 (CK5), CK6 and CK17 [50].

Van’t Veer et al. [55] analyzed expression profiling in a set of 98 breast tumors, including 18 from patients with BRCA1 germline mutations. In a first unsupervised analysis, 16 BRCA1 tumors were clustered together with another 18 sporadic tumors, all of them characterized by their ER-negative status determined by immunohistochemical staining, and all of them showing downregulation of the ER and ER target genes at the expression level. The same set of 18 BRCA1 tumors was included together with 97 sporadic tumors in the gene expression analysis performed by Sorlie et al. [52], who observed that all BRCA1-positive tumors were found to fall into the basal-like subgroup characterized by lack of expression of ER and poor prognosis and showing high expression of CK5, CK17, annexin 8, CX3CL1 and TRIM29.

Subsequent immunohistochemical studies have confirmed that a high proportion of BRCA1 carcinomas, but only a small percentage of BRCA2 carcinomas, expressed basal markers [10, 54, 56–60]. For example, Foulkes et al. [56] reported that the expression of CK5/6 was statistically associated with ER/HER2-negative BRCA1-related cancers when compared to ER/HER2-negative sporadic cancers (88% vs. 45%) in Ashkenazi Jewish women younger than 65 years of age. In addition to CK5/6, other studies have reported that the expression of the basal marker P-cadherin is more common in BRCA1-associated tumors than in familial BRCA2-associated and sporadic tumors [10, 57]. Other basal/myoepithelial markers detected with high frequency in BRCA1 tumors are vimentin [61], SPARC, caveolin-1, fascin and other [59, 61, 62].

The patterns of immunohistochemical features identified in CK5/6-positive sporadic breast cancers [low-level expression of ER, PR, BCL2, p21, p27 and HER2, combined with high-level expression of Ki-67, epidermal growth factor receptor (EGFR) and p53] [63] are similar to those observed in BRCA1-related breast cancers [31]. In contrast, BRCA2 carcinomas have immunohistochemical characteristics that are consistent with a luminal phenotype [31].

Morphological and Molecular Features of Non-BRCA1/2 Hereditary Carcinomas

Non-BRCA1/2 hereditary carcinomas represent 67% of familial breast cancers when families with only female breast cancer and 4 or 5 affected members are considered [64]. There are few studies that have defined the histological characteristics of these neoplasias [5, 10–11]. In all series, invasive ductal carcinoma was the most frequent histological type (67–78%). In 2 studies [5, 10], an excess of lobular carcinomas was found in familial non-BRCA1/2 (15%) compared with BRCA1 (3%), BRCA2 (9%) and sporadic cases (10%). The difference was only significant with respect to BRCA1 tumors. Breast cancers from familial non-BRCA1/2 patients were of lesser histological grade than BRCA1/2-associated tumors. Grade 1 tumors accounted for 27–50% of the total. In addition, non-BRCA1/2 tumors showed more tubule formation, a lower mitotic index and less pleomorphism than BRCA1/2-associated carcinomas [5, 10]

From an immunohistochemical and molecular point of view [5, 10–11], familial non-BRCA1/2 tumors are more frequently ER positive (73–75%), PR negative (54–67%) and BCL2 positive (55%), but p53 negative (78–96%); these figures clearly differ from BRCA1 tumors, but are not significantly different with respect to BRCA2 carcinomas. A variable incidence of HER2 expression and amplification (4–18%) has been found in non-BRCA1/2 carcinomas [10]. Most non-BRCA1/2 carcinomas have a luminal phenotype [65].

In 100 familial non-BRCA1/2-related breast tumors, LOH frequencies of 40% or greater were found at 1q41, 4p16, 1q23.3, 16p13, 16q24, 17p12, 21q22, 22q11 and 22q13, with the highest frequency at 22q13 [66]. Except for 22q, many of these chromosomal sites have also been highlighted in analyses of sporadic breast tumors.

By CGH, 1 study has demonstrated that the total of copy number alterations was similar in non-BRCA1/2 and sporadic tumors (9.4 and 7.7, respectively), but lower than in BRCA1-associated (12.2) and BRCA2-associated (12.5) tumors. Statistical analysis predicted that loss of 13q was one of the earliest genetic events in these non-BRCA1/2 hereditary cancers [46].

Breast Cancer in Other Breast Cancer Susceptibility Genes

As a result of the low frequency of breast carcinomas attributable to mutations in other than BRCA1- and
BRCA2-specific breast cancer susceptibility genes, it is very difficult to obtain large series in order to establish a specific phenotype for each genotype. For example, there are few reports about the morphological phenotype of tumors from CHEK2 mutation carriers, and there is no coincidence about the results. While some authors have reported that these tumors are of larger size and higher grade than tumors from patients without a CHEK2 mutation [67], others find a lower grade and more unfavorable prognostics associated with CHEK2 tumors [68]. Regarding histological subtype, no correlation has been found with the germline CHEK2 1100delC variant that is the most frequent in the North of Europe. However, it has been shown that in Poland, where there are 2 other founder variants with higher prevalence than 1100delC, the I157T mutation is associated with the lobular carcinoma subtype [69]. This is the first report demonstrating how different mutations of the same gene may be associated with specific histological subtypes of cancer. Concerning immunohistochemical characteristics, results are contradictory. While de Bock et al. [68] found positivity for ER and PR more frequently in tumors of CHEK2 carriers than in tumors of noncarriers, Kilpivaara et al. [67] found that CHEK2 tumors tend to be more frequently ER positive but that there are no differences in PR expression. At the same time, Oldenburg et al. [66], in a short series of 9 tumors, found no differences between carriers and noncarriers for ER and PR, but showed that CHEK2 tumors were more often negative for luminal CK19 staining. In all studies, CHEK2 protein expression has been found to be absent or grossly reduced in the majority of tumors from carriers of the 100delC germline variant [66, 67, 70, 71].

Germline mutations in CDH1 have been found in families with autosomal dominant susceptibility to hereditary diffuse gastric cancer (HDGC) [72–77]. HDGC has an average age of onset of 38 years for clinically detectable diffuse gastric cancer [73, 75]. Germline mutations in CDH1 are found in 30–40% of clinically defined families with HDGC from different ethnic backgrounds, predominantly from low-incidence populations of sporadic gastric cancer [75]. The CDH1 mutation spectrum is heterogeneous and includes point mutations, small deletions and insertions distributed along the entire coding sequence [76]. The identification of CDH1 mutations offers the opportunity of cancer risk reduction strategies for unaffected individuals at risk [73, 75]. Along with a risk of diffuse gastric cancer, there is an excess of lobular breast cancer in families with clinically defined HDGC [76, 77]. This is not unexpected because loss of CDH1 expression is a cardinal feature of lobular breast cancer and HDGC, and both somatic CDH1 mutations and promoter hypermethylation are found frequently in lobular breast cancer, but only rarely in infiltrating ductal carcinoma [78].

In addition to the consequences of CDH1 mutations for HDGC patients, female CDH1 mutation carriers are at increased risk of developing lobular breast cancer. Penetration studies have shown that female CDH1 germline mutation carriers have an additional risk of breast cancer, particularly lobular breast cancer, in about 39% of patients [77].

Recently, Kaurah et al. [76] have reported that within some families with founder mutations, the cumulative risk of breast cancer was 52%, which is slightly higher than the previously reported risk [77]. One family carrying the 2398delC mutation had 13 members with breast cancer; all 3 available pathology reports were confirmed to show invasive lobular breast cancer. Another family with the same mutation also had 2 breast cancer cases with 1 case confirmed as lobular breast cancer. These families had been misclassified as breast cancer families due to clustering of lobular breast cancer cases and subsequently tested negative for BRCA1/2 mutations.

**Genetic Testing and Therapeutic Implications**

Currently, age and family history are the best predictors of a high likelihood of carrying a BRCA1 mutation. However, the current strong reliance on family history may deny many women the chance to be offered genetic testing. It has been pointed out that the families with an obvious cancer syndrome are likely to represent only a small fraction of individuals with inherited predisposition to cancer. Data emerging from population-based series of early-onset breast cancer suggest that a high proportion of patients with BRCA-associated cancers present as sporadic cancers [79]. For this reason, it would be useful if other tumor or patient characteristics could be used to distinguish patients likely to carry a BRCA1 germline mutation.

After several years of research, it has been established that cancers arising in carriers of mutation in the BRCA1 and BRCA2 genes differ from each other and from sporadic breast cancer of age-matched controls. The differences are more evident and have been more extensively documented in breast cancer from BRCA1 mutation carriers. Breast cancers arising in germline carriers of BRCA1 mutations have a characteristic phenotype that
has been shown in many studies to differentiate BRCA1 tumors from sporadic tumors. Recently, it has become clear that the characteristic phenotype of BRCA1 tumors is due to expression of the basal-like phenotype [80]. This information can be used to guide, to some extent, genetic testing. For example, in the absence of a family history of breast and ovarian cancer, it has been suggested that we should suspect BRCA1 hereditary carcinoma in women diagnosed before 35 years of age that have a grade 3, ER-negative infiltrating ductal carcinoma, since the incidence of BRCA1 germline mutations in these cases is around 27% [81]. In addition, breast carcinomas should be examined for the expression of CK5/6, HER2 and EGFR, since the identification of a basal phenotype probably increases the likelihood of the patient being a BRCA1 mutation carrier, although this hypothesis remains to be tested. Lakhani et al. [81] have recently proposed a predictor model of BRCA1 status based on ER, CK5/6 and CK14 (ER negative, CK14 positive and CK5/6 positive), with better sensibility and positive predictive value than family history. According to these authors, the predictive immunohistochemical test for BRCA1 germline mutations comprising ER and CK5/6 would have a sensitivity of 56%, a specificity of 97% as well as positive and negative predictive values of 28 and 99%, respectively. In addition, the basal-like phenotype may already be currently useful in the prediction of which BRCA gene is likely to be mutated in high-risk families, where a high-risk family with basal-like cancers is much more likely to have an underlying BRCA1 mutation than BRCA2 mutation and in the classification of BRCA1 variants of uncertain pathogenicity [82].

A major limitation of the use of histopathological data in the clinical setting is the lack of specific features of BRCA2 and non-BRCA1/2 carcinomas. Most familial breast cancers are not associated with BRCA1 or BRCA2 germline mutations, and so it is of major importance to define the additional morphological and molecular markers of this group of tumors.

It is reasonable to speculate that some familial lobular breast cancers that cannot be attributed to BRCA1 or BRCA2 mutations could instead be attributed to germline mutations in CDH1 and should be reevaluated for HDGC and screened for CDH1 mutations. However, germline CDH1 mutation analysis in several non-BRCA1/2 lobular breast carcinomas, in the absence of familiar aggregation of lobular carcinomas or diffuse gastric cancer, has not revealed any genetic alterations [31, 83].

Since some hereditary tumors have specific immunohistochemical and molecular characteristics, some authors have proposed that treatment should be concordant with these specific alterations. The major role of BRCA1 is to respond to DNA damage by participating in cellular pathways for DNA repair, such as the Fanconi Anemia/BRCA pathway [84]. Because most chemotherapeutic agents function by directly or indirectly damaging DNA, the role of BRCA1 as a regulator of chemotherapy-induced DNA damage has been the subject of an increasing number of investigations. The loss of BRCA1 function is associated with sensitivity to DNA-damaging chemotherapy (mitomycin C and cisplatin) and may also be associated with resistance to spindle poisons (taxanes and vinca alkaloids) [83, 84]. The high percentage of BRCA1 tumors that overexpress the basal marker EGFR (67%) [81, 85] raises the possibility of specific anti-EGFR therapies in this particular group of patients. On the other hand, the prevalence of HER-2 amplification in BRCA1/2 tumors is low and so anti-HER2 therapies should not be recommended in these patients.

Acknowledgements

This work was supported by grants from the Spanish Ministry of Health (FIS: PI 051890; RETICS: RD06/0020/0013) and the Spanish Ministry of Science and Technology (SAF: SAF2004-08258-C02-01). M.J.R.F. and M.A.C. are postdoctoral fellows (RETICS: RD06/0020/0013) and M.A.L.-G. is the recipient of a research grant from the Fondo de Investigaciones Sanitarias (CM06/00163).

References


The Molecular Pathology of Hereditary Breast Cancer

Pathobiology 2008;75:85–94


