Genotype/Phenotype Correlations in Patients with Hereditary Breast Cancer

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Summary

Of all breast cancer cases, 5–10% can be attributed to germline mutations, and the high-susceptibility genes *BRCA1* and *BRCA2* account for about 25–28% of these cases. For the remainder, several genes of moderate and low penetrance have been discovered. Histopathologic characteristics have been studied in small cohorts, but for most of the known non-*BRCA1/2*-associated hereditary breast cancers, the histologic and immunohistochemical phenotypes are not yet identified. Particularly *BRCA1* tumors are associated with a distinct morphology and immunohistochemical characteristics that differ from sporadic breast cancer of age-matched controls. The recognition of features characteristic of these mutations can be helpful to identify patients likely to carry a germline mutation and to assess which gene should be screened for first, in families with a high occurrence of breast and ovarian cancer.

Introduction

A certain proportion of 5–10% of the breast cancer cases can be attributed to germline mutations [1]. Since the identification of *BRCA1* and *BRCA2* as the first genes with germline mutations over 20 years ago [2, 3], several other mutations associated with a higher susceptibility for the development of mammary carcinomas have been discovered.

Over the past 15 years, an increased understanding of the molecular mechanisms behind breast cancer heterogeneity has led to

the identification of genetically defined ‘intrinsic’ subtypes [4, 5] associated with different clinical outcomes [6], responses to therapy [7], and preferential sites of relapse [8].

Intrinsic Subtypes of Breast Cancer

The numerous histopathological subtypes of breast cancer and the great variability in response to therapy and clinical outcome of tumors with apparently homogenous morphology [9, 10] show the limitations of the traditional clinicopathological classification.

Transferring the findings of molecular profiling of breast cancer [4] to the everyday clinicopathological diagnostic routine, the St. Gallen consensus meeting 2011 acknowledged the immunohistochemical markers estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 as ‘surrogate markers’ for the identification of the intrinsic subtypes [11]. However, the discrimination by use of these biomarkers is a pragmatic approach aimed at the therapeutic consequences (i.e. treatment recommendations for systemic therapy proposed by the consensus meeting), as the thereby identified subtypes are similar but not identical to the intrinsic subtypes selected by gene expression analysis [11]. Today, the existence of at least 4 intrinsic subtypes is established.

The *luminal subtype* is characterized by expression of the ER and of other genes that encode proteins characteristic of the luminal epithelial cells [9]; up to 60% of breast cancers fall into this category [12]. Depending on the expression levels, a further subdivision into the luminal A and luminal B subgroups is made (fig. 1) [6, 9]. Luminal A tumors are characterized by high expression of estrogen-related and low expression of proliferation-related genes, whereas luminal B tumors are characterized by lower expression of estrogen-related and low expression of PR genes and higher expression of proliferation-related genes [6]; these profiles can be reproduced by immunohistochemistry.

Fig. 1. Luminal subtypes of breast cancer. (Left) Luminal A breast cancer, (right) luminal B breast cancer. Hematoxylin and eosin staining, 100 × magnification, each with corresponding Ki-67 immunohistochemistry (insert, 200 × magnification).

Fig. 2. Carcinoma with medullary features. Example for the morphologic characteristics of *BRCA1* tumors. Pushing margins, prominent lymphoid infiltration (overview left), geographic areas of necrosis may be present. Marked cellular atypia with distinct nucleoli and high mitotic index (detail right). Hematoxylin and eosin staining, 25 × and 200 × magnification.

The *basal-like subtype* accounts for 15–20% of breast cancers [12] and is named for its expression of genes characteristic of the basal-myoeptithelial cells of the normal breast [4, 9]. A defined immunohistochemical profile for the identification of this subtype does not exist, but basal-like carcinomas typically lack expression of hormone receptors or HER2 (‘triple negative breast cancer’) [9], so that the majority of basal-like cancers can be classified as triple negative and vice versa, with a concordance of approximately 80% (18–40% of basal-like cancers do not have a triple-negative phenotype on immunohistochemical analysis) [13–15].

About 10–15% of breast cancers belong to the subgroup of *HER2-enriched tumors* [5, 12], which are characterized by high expression levels of genes located in the HER2 amplicon on 17q21 [9].

Pathological Characteristics of Hereditary Breast Cancers

Of all human breast cancers, hereditary forms represent a minor percentage (5–10%). Taken together, the high-susceptibility genes *BRCA1/2* are responsible for about 25–28% of the hereditary breast cancer cases [16, 17]; other germline mutations of high, intermediate, and low penetrance account for about 20% of the breast cancer cases [17]. In summary, for over 50% of the hereditary breast cancer cases, no mutation has as yet been identified. It is not likely that another high-penetrance gene (comparable to *BRCA1* or *BRCA2*) will be found for this group; the familial risk is probably due to multiple genes of lower penetrance (polygenic model) [18] or a germline mutation in a moderate-penetrance gene still to be identified [17].

The *BRCA1* gene was first identified in 1990 by Hall et al. [2]. It localizes to the long arm of chromosome 17 (17q21) and is involved in the regulation of the cellular response to DNA damage by mediating the repair of double-strand breaks through homologous recombination [1, 19]. It is estimated that carriers of *BRCA1* mutations have a cumulative risk of 57% for the development of breast cancer and of 40% for ovarian cancer by the age of 70 years [20]. Other cancers associated with *BRCA1* mutations include prostate cancer, pancreatic cancer, and cancer of the uterine body and cervix [21].

In terms of histological types, most *BRCA1*-associated breast cancers are invasive ductal adenocarcinomas of no special type (NST) and of higher grade than sporadic breast cancers [1, 22, 23]. They have higher mitotic indices and show a high frequency of necrotic areas and a higher proportion of continuous pushing margins and lymphocytic infiltration [1]. Interestingly, there is a remarkable overrepresentation of carcinomas with medullary features in the *BRCA1* group (13% ‘medullary carcinomas’ vs. 2% controls) and, additionally, a large proportion of *BRCA1* carcinomas exhibit some medullary features (hence meeting the diagnostic criteria for ‘atypical medullary carcinomas’) [24]. Carcinomas with medullary features comprise a histological subtype demonstrating all or some of the following characteristics: poor differentiation, high mitotic count, solid sheet-like growth pattern with well-defined pushing borders, and diffuse lymphocytic infiltration [25] (fig. 2). They are associated with a particularly favorable prognosis, probably due to a low incidence of lymph node metastasis [25, 26]. Eisinger et al. [26] found that a proportion of 11% of the ‘medullary carcinomas’ carry *BRCA1* germline mutations.

Concerning immunohistochemical markers of prognostic and predictive relevance, Mavaddat et al. [27] observed in a large data set of 4,325 BRCA1 mutation carriers that 78% of the tumors were ER negative; overexpression of HER2 could be shown in approximately 10% of the cases and 69% were triple negative. The high mitotic count was corroborated by a high proliferation index (i.e. nuclear Ki-67 staining of > 20% of the tumor cells) [23].

Compared to sporadic tumors, BRCA1-associated tumors more often express several markers characteristic of basal/myoepithelial breast cells, including cytokeratin (CK)5/6, CK14, caveolin, vimentin, laminin, P-cadherin, osteonectin, and the epidermal growth factor receptor (EGFR) [28, 29]. In terms of the intrinsic subtypes, the majority of the BRCA1 breast cancers can thus be classified as basal like [1, 17]. Furthermore, BRCA1 tumors more often stained p53 positive in comparison to sporadic tumors [1, 23], probably reflecting the higher frequency of mutations in the *TP53* gene found in BRCA1 tumors [30, 31].

The *BRCA2* gene maps to the long arm of chromosome 13 (13q12–13). It is involved in the maintenance of genomic stability, specifically in the error-free repair of double-stranded DNA breaks through homologous recombination [1, 32]. Carriers of *BRCA2* mutations have a cumulative risk of approximately 49% of developing breast cancer and of 18% for developing ovarian cancer by the age of 70 years [20]. Other associated malignancies include male breast cancer, cancer of the fallopian tube, prostate cancer, gastrointestinal cancers (pancreas, gall bladder, bile duct, stomach) and malignant melanoma of the skin [1, 33].

Like BRCA1-associated tumors and sporadic carcinomas, breast cancers arising in *BRCA2* mutation carriers are mostly invasive ductal adenocarcinomas of NST with a moderate or poor differentiation, high mitotic counts, and continuous pushing margins [1, 22, 23]. There is contradictory information regarding an association with a special histologic subtype. Some authors reported a higher incidence of pleomorphic lobular carcinomas [34] while in other collectives a statistically significant association to a histological subtype could not be observed [24, 35].

Immunohistochemically, *BRCA2* tumors seem to be more similar to sporadic tumors. Mavaddat et al. [27] found ER negativity in 23% of tumors arising in *BRCA2* mutation carriers, HER2 overexpression in approximately 10%, and triple negativity in 16%, when investigating a large collective of 2,568 *BRCA2* mutation carriers. The overexpression of ER, PR, CK8, and CK18 assigns *BRCA2* tumors to the luminal intrinsic subtype [1, 23], with the vast majority belonging to the luminal B subtype [36, 37].

Non-*BRCA1/2*-associated hereditary breast cancers are responsible for the remaining 72–75% of familial cases. All in all, half of the cancer-related genes in hereditary breast cancer are still unidentified [17]. Many cancer syndromes and germline mutations are currently under investigation for their potential morphologic correlations [38].

The *RAD51C* gene is a rare high-penetrance breast and ovarian cancer susceptibility gene which encodes a DNA double-strand break repair protein and is localized on the long arm of chromosome 17 (17q23) [39]. Meindl et al. [39] identified several

pathogenic *RAD51C* mutations in *BRCA1/2* mutation-negative hereditary breast and ovarian cancer families. In their collective, the mean onset of breast cancer was 53 years, and the majority of the patients had intermediate-grade invasive ductal carcinoma, mostly hormone receptor positive and HER2 negative, indicating more favorable histopathological features in comparison to *BRCA1*-associated breast cancer. These findings were corroborated by Gevensleben et al. [23] who compared a large cohort of *RAD51C*-mutated breast cancer cases to breast cancer cases harboring *BRCA1* and *BRCA2* mutations in regard to clinicopathological and immunohistochemical features and found a resemblance to *BRCA2*-related cancers. Regarding the immunohistochemical profile of *RAD51C* breast cancers, Gevensleben et al. [23] observed high levels of luminal CKs, E-cadherin, activating enhancer binding protein 2 (AP-2) alpha and AP-2 gamma. In direct comparison to *BRCA2*-associated breast cancers, the proliferation marker Ki-67 was found to be the only discriminating feature, with significantly higher expression in *BRCA2*-associated breast cancers, indicating that *RAD51C*-related breast tumors belong to the intrinsic subtype of ‘luminal A’ breast cancers and thus are associated with a more favorable outcome. The lack of features characteristic of the *BRCA1* phenotype, such as marked p53 expression or histopathological criteria of the medullary subtype, was also noted by the authors [23].

The *CHEK2* gene (coding for checkpoint kinase 2) is a tumor suppressor gene located on the long arm of chromosome 22 (22q12.1) [40]. It encodes a nuclear protein which, in response to DNA damage (i.e. double-strand breaks), is phosphorylated by ATM and subsequently catalyzes the phosphorylation of several substrates, thereby regulating cell cycle progression and protecting cells against too rapid, uncontrolled growth [40–42].

Mutations of *CHEK2* predispose to several types of common cancer, e.g. breast cancer and prostate cancer [43, 44]. Several different *CHEK2* mutations have been described [40, 42], 5 of which have been associated with increased breast cancer risks. These *CHEK2* variants appear to confer moderate breast cancer risks (2–4-fold) and seem to vary widely among different geographical and ethnic populations [45]. Domagala et al. [42] investigated the association between *CHEK2* mutations and the immunophenotypic intrinsic subtypes of breast cancer in a large collective of *CHEK2* mutation carriers and controls. They found that *CHEK2*-associated cancers were predominantly luminal, with significant associations of the *CHEK2*-I157T variant with the luminal A subtype, and of truncating *CHEK2* mutations with the luminal B subtype. In a collective of 26 breast tumors from *CHEK2* 1100delC carriers analyzed by Nagel et al. [46], all tumors could be assigned to the luminal intrinsic subtype (8 tumors luminal A, 18 tumors luminal B). With respect to histopathological characteristics, an association between lobular carcinoma and the I157T missense mutation was reported by different authors [47, 48]. It was observed that *CHEK2*-associated tumors were more likely to be of multicentric origin and presented as larger tumors (> 2 cm) [48].

Conclusions

For the identification of mutation carriers, age at the time of tumor diagnosis and family history are the best predictors [22]. To identify the responsible gene, histopathologic evaluation can be crucial, as especially BRCA1 breast cancers are associated with distinct morphology and immunohistochemical characteristics and differ from sporadic breast cancers of age-matched controls [22]. Studies have demonstrated that the inclusion of morphologic and immunohistologic breast cancer characteristics in models of risk estimation improves the accuracy in predicting the BRCA status [28, 49]. The German S3 medical guideline for diagnosis, therapy and follow-up care of breast cancer proposes that the pathologist should report the possibility of a hereditary background when encountering suggestive histopathological features. Non-BRCA1/2 mutations are responsible for the majority of hereditary breast cancer cases; the known non-BRCA1/2-associated hereditary breast cancers

comprise a heterogeneous group of tumors, for most of which the histologic and immunohistochemical phenotypes are yet to be identified. Due to the low frequencies of these mutations, it is difficult to obtain sufficiently large collectives to be able to establish a phenotype. Moreover, it has been postulated that a large percentage of the familial clustering in breast cancer might be due to a polygenic setting, with several moderate- and/or low-risk breast cancer susceptibility alleles conferring significantly increased breast cancer risks [45, 50, 51]. Individual family trees with the involvement of several breast cancer susceptibility genes adding up to an overall increased risk might make it difficult to identify characteristic histological profiles for the remainder of the hereditary breast cancer cases.

Disclosure Statement

The authors declare no conflict of interest.

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