Review
The pathology of familial breast cancer
The pre-BRCA1/BRCA2 era: historical perspectives
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Abstract

A proportion of breast carcinomas develop as a result of a genetic predisposition to the disease. Prior to cloning of the BRCA1 and BRCA2 genes a limited number of studies were carried out to identify specific histopathological characteristics of hereditary breast cancer. These studies are the subject of this review. The main finding was the association of the (atypical) medullary type of breast cancer with a family history; the most important caveat being that medullary breast cancer is found more frequently in young patients. In view of the frequent bilateral occurrence of lobular cancer, this histologic type is also likely to be associated with a predisposing genetic defect. Future investigations will have to test this hypothesis. In addition to mutations in the BRCA1 and BRCA2 genes, there are as yet unidentified genetic defects predisposing to breast cancer development, and histopathology may well help in identifying these genes in the future.

Keywords: association, breast, carcinoma, familial, histopathology

Introduction

Anecdotal evidence from individual families in which breast cancer occurs very frequently and large epidemiological studies have shown that some women have a familial predisposition to breast cancer. The anecdotal evidence includes the pedigree of Broca’s family [1]. He was a famous French surgeon (1824–1880), and in his family tree (which comprised over five generations) 10 out of 24 women died of breast cancer. Systematic epidemiological studies performed in the second half of the 20th century have shown that, in women with a family history of breast cancer, the risk of breast cancer is increased two- to threefold (‘familial breast cancer’). Such studies have also shown that there are families in which breast cancer risk is inherited in an autosomal-dominant fashion (‘hereditary breast cancer’). In recent years, it has been shown that germline mutations in the BRCA1 and BRCA2 genes account for a large proportion of cases of hereditary breast cancer.

Histopathological findings and careful autopsy examination have played a major role in the recognition of many familial cancer syndromes [2], including multiple endocrine neoplasia type II and Beckwith–Wiedemann syndrome. The creation of tissue archives that include a coded index of patient details, tissue and diagnosis at a time when the possibilities for its use were remote has placed pathologists in a unique position to play a central role in familial breast cancer research. The knowledge of the histopathological features will also help in understanding the genetic defects that underlie the various forms of familial predisposition. Histopathological diagnosis and tissue archives may therefore be of fundamental importance in our understanding of familial breast cancer, and hospitals would be wise to look after this unique resource.

This review describes histopathological studies with regard to specific histological features of breast carcinoma in patients who have developed this disease as part of what was
described as ‘familial breast cancer’ or ‘hereditary breast cancer’ before the identification of the \textit{BRCA1} and \textit{BRCA2} genes. The histological features of breast carcinomas arising in patients with germline mutations in the \textit{BRCA1} or \textit{BRCA2} genes are discussed in this issue by Lakhani.

In addition to mutations in the \textit{BRCA1} and \textit{BRCA2} genes, there are as yet unidentified genetic defects that predispose to breast cancer development, and histopathology may well help in identifying these genes in the future.

\textbf{Histopathology of breast cancer in patients with a family history of breast cancer}

Breast cancer is a very heterogeneous disease that is characterized by a number of histopathological subtypes. The major histological types of breast cancer and an estimate of their relative contribution are shown in Table 1. As can be seen from this table, the vast majority of breast carcinomas fall into the category ‘ductal, not otherwise specified’; of note is that the tumours in this category still show heterogeneous morphology. Ductal carcinomas not otherwise specified can be divided into subgroups with different grades of malignancy on the basis of degrees of differentiation, pleomorphism and mitotic activity.

Breast cancer is a common disease, occurring in approximately one in 12 European or North American women. In part, clustering of breast cancer in a family is a result of chance, because breast cancer is so frequent; in some families, the clustering is the result of shared environmental risk factors; and in a proportion of families an underlying genetic defect will be the culprit. Before the identification of the \textit{BRCA1} and \textit{BRCA2} genes, it was impossible to discriminate between these possibilities. This still applies to all other as yet unidentified genetic defects that predispose to breast cancer.

There have been a limited number of studies that have described histopathological features in association with the presence of a family history. In a comprehensive review of the literature through the early 1980s, Mulcahy and Platt [3] concluded that most studies have been extremely small or did not represent population-based samples. Since then, there have been two large population-based studies [4**,5**]. The main features and conclusions of these two studies are summarized in Table 2.

In addition to family history, a number of other patient characteristics have been found to be associated with histological type. For example, patients with medullary breast cancer have been reported to be younger than those with other histological types, and medullary carcinomas have been reported to be more frequent in blacks than in whites [5**]. A comprehensive review of the histopathology of familial breast cancer and of breast cancer in young women was presented by Marcus \textit{et al} [6*].

\begin{table}[h]
\centering
\begin{tabular}{|l|l|}
\hline
Histologic type & Estimated frequency (%) \\
\hline
Ductal carcinoma, not otherwise specified & 70 \\
Lobular carcinoma & 10 \\
Tubular carcinoma & 5 \\
Mucinous carcinoma & 5 \\
Medullary carcinoma & 3 \\
Atypical medullary carcinoma & 3 \\
Other (metaplastic, papillary, adenoid cystic, etc) & 4 \\
\hline
\end{tabular}
\caption{Histological classification of invasive breast cancer, including the estimated proportion of all breast carcinomas for each histologic type}
\end{table}

Historically, familial breast cancer has been found to be associated with medullary carcinoma, tubular carcinoma and lobular carcinoma. These are considered briefly below.

\textbf{Medullary carcinoma}

In patients who had a mother with breast cancer, Rosen \textit{et al} [4**] found medullary cancer in 16% and atypical medullary cancer in 18% of women. Of note is that these authors did not find an increased frequency of medullary cancer in patients who had a sister with breast cancer, an observation that was also made by Anderson in 1994 [6]. Claus \textit{et al} [5**] found an increased frequency of medullary cancer in young women, but no association with family history. An important caveat with respect to the diagnosis of medullary carcinoma is that there is considerable interobserver variability in making this diagnosis. It is clear, however, that tumours with features that are consistent with medullary carcinoma are more frequent in patients with a family history and in younger patients. Probably the most important property of these tumours is a high proliferative activity, resulting in a tumour with pushing margins and high mitotic count.

\textbf{Tubular carcinoma}

Lagios \textit{et al} [7] identified 17 tubular cancers in mastectomy specimens from a cohort of 211 breast cancer patients. A family history that was positive for mammary carcinoma in a first-order relative was recorded for six out of 15 patients analyzed (40% versus 16% in the patients with other histological types of breast cancer).

\textbf{Lobular carcinoma in situ and invasive lobular carcinoma}

Among the histopathological types of breast cancer, lobular cancer stands out as a candidate for a tumour caused by a genetically inherited predisposition. The main reason for this is the high frequency of bilateral invasive and \textit{in situ} lobular breast cancer. Claus \textit{et al} [5**] found
that patients with lobular carcinoma \textit{in situ} were more likely than patients with other histopathological types of breast cancer to have a mother and/or sister who had breast cancer. In their series, lobular carcinoma \textit{in situ} was bilateral in 27\% of cases [5**]. Rosen \textit{et al} [4**] found that 17\% of patients who had one or more sisters with breast cancer were of lobular histologic type.

It is likely that lobular cancer develops as part of an inherited predisposition, and that this is due to low penetrance gene(s). Mutations in the \textit{E-cadherin} gene can be identified in the majority of lobular carcinomas. These mutations are all somatic mutations, however, and germline mutations have not been identified in patients with lobular cancer [8,9].

\textbf{Can preneoplastic histopathological breast alterations be identified in familial breast cancer?}

A number of histologic alterations of the breast have been identified, which are associated with an increased risk of developing breast cancer. These histologic alterations include epithelial hyperplasia, atypical ductal hyperplasia [10], fibroadenoma with 'complex features' [11], scar lesions [12] and cysts [13]. These conditions are all associated with an increased risk of developing breast cancer in both breasts (and not only in the breast from which the tissue showing these histological alterations has been excised). To date, there is no evidence that they are direct precursors of breast carcinoma, and they should be viewed as markers of increased risk. The mechanism that underlies the association of these lesions with increased risk of breast cancer development is currently unknown. If epithelial hyperplasia, atypical ductal hyperplasia, fibroadenoma with 'complex features' or scar lesions are present, the risk of developing breast cancer is roughly doubled if there is also a family history of breast cancer. Fine needle aspiration from all four quadrants of both breasts has been performed in women without breast abnormalities [14], and it was noted that an increased frequency of 'atypical ductal hyperplasia' was found in women with a family history of breast cancer compared with women without a family history. As has also been pointed out in other reviews in this issue, atypical ductal hyperplasia is a histological diagnosis that cannot been made on the basis of cytological examination. Therefore, these findings cannot be taken as evidence that preneoplastic conditions can be diagnosed in women with a familial predisposition to develop breast cancer.

Ductal and lobular carcinoma \textit{in situ} are the only known direct precursor lesions to breast cancer, and ductal carcinoma \textit{in situ} has not been reported in association with breast cancer family history. In a series of 605 bilateral prophylactic mastectomies performed because of a family history of breast cancer [15], not one case of carcinoma \textit{in situ} was found.

It must be realized that it is difficult to find microscopic precursor lesions to invasive breast cancer if these lesions cannot be detected using mammography or magnetic resonance imaging. The pathological examination of a prophylactic mastectomy specimen will include taking several sections from macroscopically normal parts of the breast, usually resulting in examination of less than 1\% of all breast tissue. Because it is to be expected that cancer will start in one (microscopic) area of the breast (which is also the case when there is a germline gene mutation predisposing to breast cancer), the risk of finding such a minute lesion is small. Germline mutations in \textit{BRCA1}, \textit{BRCA2} and other genes could theoretically also lead to multiple or even diffuse histological alterations (for instance multiple foci of proliferation of dysplastic epithelium, analogous to multiple polyps in familial adenomatosis coli). Such diffuse alterations in the breast have not been identified to date, however, and it is very unlikely that they are present.

\textbf{Breast cancer histopathology in other cancer syndromes}

Cancer syndromes that are also associated with an increased risk of developing breast cancer include Cowden's disease, the Li-Fraumeni cancer syndrome and ataxia–telangiectasia. No studies of the histopathological features of breast carcinomas that occur in patients with these syndromes have been published.
Conclusion
Before the cloning of the BRCA1 and BRCA2 genes, a number of studies reported an association of histopathological type with a family history, but these studies have been difficult to interpret due to the small number of samples and differing criteria for 'positive family history' and pathological typing. Hence, there are only limited data on specific histologic patterns in breast carcinomas that are associated with hereditary and familial breast cancer. The main finding was the association of the medullary type of breast cancer with a family history; the most important caveat being that medullary breast cancer is found more frequently in young patients. As is seen elsewhere in this review series, the association of family history with medullary breast cancer is now confirmed by studies based on knowledge of BRCA1 and BRCA2 mutation status.

In view of the frequent bilateral occurrence of lobular cancer, this histological type is also likely to be associated with a predisposing genetic defect. Future investigations will have to test this hypothesis.

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