

Review

The pathology of familial breast cancer Clinical and genetic counselling implications of breast cancer pathology

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Abstract

Approximately 5% of all breast cancers are due to one of the high-risk breast cancer genes *BRCA1* and *BRCA2*, or possibly to a third or fourth moderate- to high-risk gene(s). A further proportion of cases arise in the presence of a less striking family history, with later average age at onset and lower penetrance: familial breast cancer. Bilaterality is a recognized feature of hereditary breast cancer. Cancers often present at an early age, with the contralateral risk high within 10 years. Proof that bilateral malignancies are separate primaries can be difficult histologically, however, especially within 3 years. The recent finding of specific pathological features related to *BRCA1* and, to a lesser extent, *BRCA2* mutations means that, in addition to bilaterality and family history, a pathological element can be entered into the risk calculation for the presence of *BRCA1/BRCA2* mutations. This will facilitate the targeting of mutation testing to families in which a positive result is most likely, and may subsequently influence the clinical management of these families.

Keywords: *BRCA1*, *BRCA2*, genetic testing, ovarian cancer, prophylactic mastectomy

Breast cancer genetics

A number of genes have been identified during the past 10 years which, when inherited in a mutant form, confer a high lifetime risk for breast cancer and for a spectrum of other cancers. These genes are not common and together are estimated to occur in a mutated form in about one in 300 individuals in the general population [1,2], and to account for about 5% of all breast cancers. The proportion of young breast cancers accounted for by these high-risk genes is, however, considerably higher [3]. In addition to these high-risk susceptibility genes, there are also likely to be a number of lower penetrance, more frequently occurring gene mutations that increase breast cancer risk. These probably interact significantly with epidemiological risk factors [4]. Few such genes or polymorphisms have been identified as yet.

The breast cancer genes

BRCA1 was mapped to chromosome 17q in 1990 [5] and the genetic sequence was published in 1994 [6], simultaneously with a report of the localization of a second major susceptibility gene *BRCA2* [7]. *BRCA2* was cloned in 1995 [8]. These genes are both large and mutation analysis is expensive and time consuming. Nonetheless, in families with a high chance of a genetic predisposition, genetic testing is offered in most Western genetics centres. Thus, an increasing number of young women with a strong family history of breast and ovarian cancer are undergoing presymptomatic genetic testing.

Somatic mutations in the *TP53* gene are extremely common in all types of cancer. Inherited germline muta-

tions are, however, rare. The Li-Fraumeni syndrome (LFS) represents the striking pattern of childhood malignancy (typically soft tissue and osteosarcomas, gliomas or adrenocortical carcinoma) and very early onset breast cancer (50% of female gene carriers have developed breast cancer by 30 years of age). Over 70% of classical LFS families have inherited *TP53* mutations [9*]. There is good in-vitro evidence to suggest that patients with LFS have an abnormal response to low-dose radiation with defective apoptosis [10]. Recognition of this syndrome is therefore important, not least because it has implications for breast-screening methods.

Other recently discovered genes that confer an increase in risk of breast cancer and are associated with bilateral benign and malignant breast disease are Cowden's disease (due to mutations in the *PTEN* gene [11]) and Peutz-Jehger syndrome (PJS; due to mutations in *CDNK4* [12]). Both are rare, and the lifetime risk of breast cancer is probably less than 35%. Both these conditions have a distinct clinical phenotype with a diagnosis possible on clinical grounds (mucosal pigmentation in PJS; macrocephaly, scrotal tongue and thyroid tumours in Cowden's disease) and on pathology of skin and gut tumours (typical hamartomas of the gut in PJS and trichilemmomas in Cowden's disease).

It is difficult to predict whether *BRCA1* or *BRCA2* mutations are present in most families with multiple cases of breast cancer. The presence of two or more ovarian cancers in addition to two or more breast cancers diagnosed before the age of 60 years gives at least a 90% likelihood of *BRCA1* mutation, and male breast cancer plus three or more breast cancers diagnosed before the age of 60 years gives an 80% risk of *BRCA2* [13]. These particular families, however, represent less than 0.5% of all breast cancer and probably less than 10% of all *BRCA1/BRCA2* families. In particular, families with only two or three breast cancers diagnosed before the age of 60 years have a relatively small risk of a *BRCA1/BRCA2* mutation, and the majority of the hereditary element is due to other, as yet unidentified, genes [13]. Therefore, information from the breast cancer pathology may help prioritize those families in which genetic screening of *BRCA1/BRCA2* would be most useful.

Pathology of hereditary breast cancer

Hereditary breast cancer has some interesting biological differences compared with apparently sporadic cancer. In breast malignancies from patients with a *BRCA1* mutation, a greater proportion are high grade and histologically medullary or atypical medullary in type [14,15*].

Therefore, in individuals with bilateral medullary/atypical medullary cancer, the probability of *BRCA1* mutation should be very high. This will need to be confirmed by further studies. At the present time, no other histopatho-

logical type is associated with mutations in particular susceptibility genes. Nonetheless, finding bilateral breast cancers or multiple primary tumours will increase the chance of hereditary disease.

Both lobular carcinoma *in situ* (LCIS) and atypical hyperplasia have been associated with family histories of breast cancer [16,17]. The 10 year risk of invasive disease in association with family history is approximately 40% [17]. Skolnick *et al* [16] suggested that persons with LCIS were more likely to have a mother or sister with breast disease than with other tumour types. The Breast Cancer Linkage Consortium [15*], however, demonstrated that LCIS was less common in carriers of *BRCA1* and *BRCA2* mutations than in sporadic control individuals, although this did not reach formal statistical significance. Skolnick *et al* [16] did not find a significant statistical association between ductal carcinoma *in situ* (DCIS) and family history. This was supported by the Breast Cancer Linkage Consortium data, which found fewer cases of DCIS among *BRCA1* mutation carriers than among control individuals. The rate of DCIS in *BRCA2* mutation carriers was similar to that in sporadic control individuals, however. It may be that proliferative breast disease is a marker for *BRCA3/BRCA4*.

The evidence from histological studies for the association of specific types of tumour with *BRCA1* and *BRCA2* mutations will allow a directed approach to genetic testing of breast cancer families.

The survival of women with breast cancers with known mutations in *BRCA1/BRCA2* is controversial. Early reports based on families linked to *BRCA1* [18] suggested that the survival for these women was significantly better than that in matched individuals with sporadic tumours. This study had a survival bias, however; in order to ascertain large families for genetic linkage, a number of women within the family need to survive. Other studies have suggested that the survival is worse in *BRCA1* and *BRCA2* mutation carriers [19], or the same [20,21]. A more recent study [22] of Ashkenazi Jews with mutations in *BRCA1/BRCA2* demonstrated that carriers did not seem to have either a better or worse prognosis. Larger prospective studies are needed to answer fully the question of survival among this group of women with breast cancer.

Genetic testing

A number of groups have reported on the likelihood of finding *BRCA1* and to a lesser extent *BRCA2* mutations in certain given situations with different family histories [23,24]. The new information from breast pathologists will almost certainly alter the approach. Although the chances of finding a *BRCA1* mutation in an individual with a sporadic breast cancer who is aged under 50 years is small [25], this would alter significantly if medullary features were found, particularly in the presence of a family history

of breast or ovarian cancer. Most genetic testing occurs in the context of an unaffected woman seeking advice about her risks of breast cancer. Therefore, the pathology of the breast cancers in her relatives will be relevant. Finding a histology report with medullary features or that all the breast cancers in the family were oestrogen receptor negative and grade 3 would heighten the chance of finding a mutation in the family, thus enabling further management guidance of the individual at risk. Even if the woman does not want to know her own *BRCA1/BRCA2* status [26*], she may still want to take advantage of ovarian screening because she would be at half the carrier risk for ovarian cancer of 20–60% [2].

Breast cancer management

Once breast cancer develops in an individual, appropriate management of that cancer is the primary consideration. Because many of these patients are young and present with early cancers, breast conservation is in many cases technically possible. Wide local excision and axillary node sampling (at least) with adjuvant radiotherapy might be expected to produce equivalent results to simple mastectomy if this disease is similar in all respects to sporadic breast cancer. For a woman with either a proved or suspected genetic susceptibility, the chance of recurrence must take into account the background susceptibility of the remaining breast tissue. This includes the risk of a new primary in the contralateral breast. In order to discuss this, an estimate of the risk involved is required. Because familial cancers are more likely to be multifocal and bilateral, the risk of a new primary on the treated side is likely to be high without adjuvant therapy. There are very little data on the conservative management of *BRCA1/BRCA2* mutation carriers compared with those with sporadic disease, although the outcome of breast conservation in a small number of hereditary versus sporadic early age breast cancers in an American cohort [27] has been reported. At present, there is no clear contraindication to breast conservation for the affected breast.

Management of the contralateral breast

The risk to the contralateral breast for a woman with breast cancer and a hereditary predisposition approaches 50% at 10 years [28]. The greatest chance of recurrence of breast cancer, either locoregional or metastatic, is in the first 2 years after diagnosis. Given the high contralateral risk, many women with a *BRCA1/BRCA2* mutation (or a high risk for carrying a mutation) may opt for prophylactic removal of the contralateral breast in addition to mastectomy for the ipsilateral side. A further option is close surveillance of the remaining breast tissue. Screening for early breast cancer is of uncertain benefit in terms of a clear reduction in mortality, however [29,30], although early cancers can undoubtedly be detected [31–33]. Conventional mammographic screening may be less sensitive in the younger breast [30], but this remains unclear.

Screening for breast cancer

Whereas screening by mammography has been accepted in the UK for women over the age of 50 years [34], screening under this age is still controversial. A number of studies [31,33] suggest that screening women with a family history of breast or ovarian cancer is of use. If a woman has bilateral medullary carcinoma of the breast, even in the absence of any further family history, it becomes likely that the malignancy is due to a *BRCA1* mutation. Unaffected women in this type of family should then be offered mammographic screening. Because tumours associated with *BRCA1* mutations are highly proliferative, screening intervals would have to be adjusted to avoid interval cancers. The pathology of breast cancers can therefore be used to direct clinical screening of families as well as genetic screening.

Further studies

We would suggest that the following studies should be undertaken in the future in order to clarify further the correlation between breast cancer pathology and family history/*BRCA* mutations:

- (1) a long term prospective study of the pathology of breast tumours in families with known *BRCA* mutations;
- (2) analysis of *BRCA1* in an unselected series of medullary carcinoma;
- (3) assessment of families with proliferative breast disease for the potential involvement of future *BRCA* genes; and
- (4) The inclusion of pathology data into the risk evaluation equation in families already tested for *BRCA1/BRCA2* mutations.

Conclusion

Although options for women diagnosed with breast cancer in the presence of a family history may seem limited and the evidence to support each option relatively thin, many women recently diagnosed are now requesting genetic tests to guide their decisions and those of their family. The pathology of their breast cancer may give further useful information in deciding which samples represent a high priority for genetic testing.

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