Review

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

Fiona Lalloo and D Gareth R Evans

Christie Hospital, Manchester, UK

Received: 30 August 1999
Revisions requested: 16 September 1999
Revisions received: 6 October 1999
Accepted: 13 October 1999
Published: 27 October 1999

Important note about how to cite this article
This article is also available online in the *Breast Cancer Research* website. To avoid confusion, please ensure that only the online version of the article is cited in any reference, as follows:
Lalloo F, Evans DGR: The pathology of familial breast cancer: clinical and genetic counselling implications of breast cancer pthology [review]. http://breast-cancer-research.com/vol1no1/27oct99/review/5

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-

DCIS = ductal carcinoma *in situ*; LCIS = lobular carcinoma *in situ*; LFS = Li-Fraumeni syndrome; PJS = Peutz-Jehger syndrome.

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*/*BCRA2* 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 histopathological 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.

References

Articles of particular interest have been highlighted as:
- • of special interest
- •• of outstanding interest

1. Claus EB, Risch NJ, Thompson WD: **Age at onset as an indicator of familial risk of breast cancer.** *Am J Epidemiol* 1990, **131**:961–972.
• CASH studies provide excellent epidemiological data for familial breast cancer.

2. Ford D, Easton DF Peto J: **Estimates of the gene frequency of BRCA1 and its contribution to breast and ovarian cancer incidence.** *Am J Hum Genet* 1995, **57**:1457–1462.

3. Langston AA, Malone KE, Thompson JD, Daling JR, Ostrander EA: **BRCA1 mutations in a population-based sample of young women with breast cancer.** *N Engl J Med* 1996, **334**:137–142.

4. Easton D: **Breast cancer genes-what are the real risks?** *Nature Genet* 1997, **16**:210–211.

5. Hall JM, Lee MK, Newman B, *et al*: **Linkage of early-onset familial cancer to chromosme 17q21.** *Science* 1990, **250**:1684–1689.

6. Miki Y, Swensen J, Shattuck-Eidens D, *et al*: **A strong candidate for the breast and ovarian cancer susceptibility gene, BRCA1.** *Science* 1994, **266**:66–71.

7. Wooster R, Neuhausen SL, Mangion J, *et al*: **Localization of a breast cancer susceptibility gene, BRCA2, to chromosome 13q12-13.** *Science* 1994, **265**:2088–2090.

8. Wooster R, Bignell G, Lancaster J, *et al*: **Identification of the breast cancer gene BRCA2.** *Nature* 1995, **378**:789–791.

9. • Varley JM, Evans DGR, Birch JM: **Li-Fraumeni Syndrome: a molecular and clinical review.** *Br J Cancer* 1997, **76**:1–14.
Good review of Li-Fraumeni syndrome.

10. Boyle JM, Greaves MJ, Camplejohn RS, *et al*: **Radiation induced G(1) arrest is not defective in fibroblasts from Li-Fraumeni families without TP53 mutations.** *Br J Cancer* 1999, **79**:1657–1664.

11. Marsh DJ, Coulon V, Lunetta KL, *et al*: **Mutation spectrum and genotype-phenotype analyses in Cowden disease and Bannayan-Zonana syndrome, two hamartoma syndromes with germline PTEN mutations.** *Hum Mol Genet* 1998, **7**:507–516.

12. Hemminki A, Markie D, Tomlinson I, *et al*: **A serine/threonine kinase gene defective in Peutz-Jeghers syndrome.** *Nature* 1998, **391**: 184–187.

13. Ford D, Easton DF, Stratton M, *et al*: **Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families.** *Am J Hum Genet* 1998, **62**:676–689.

14. Armes JE, Egan AJM, Southey MC, *et al*: **The histologic phenotypes of breast carcinoma occuring before age 40 years in women with and without BRCA1 and BRCA2 germline mutations.** *Cancer* 1998, **83**:2335–2345.

15. • Breast Cancer Linkage Consortium: **Pathology of familial breast cancer: differences between breast cancers in carriers of BRCA1 or BRCA2 mutations and sporadic cases.** *Lancet* 1997, **349**: 1505–1510.
Overall review of the pathology of BRCA1/BRCA2 tumours.

16. Skolnick MH, Cannon-Albright L, Goldgar DE, *et al*: **Inheritance of proliferative breast disease in breast cancer kindreds.** *Science* 1990, **250**:1715–1720.

17. Dupont WD, Page DL: **Risk factors for breast cancer in women with proliferative breast disease.** *N Engl J Med* 1985, **312**:146–151.

18. Porter DE, Cohen BB, Wallace MR, *et al*: **Breast cancer incidence, penetrance and survival in probable carriers of BRCA1 gene mutation families linked to BRCA1 on chromosome 17q12-21.** *Br J Surg* 1994, **81**:1512–1515.

19. Foulkes W, Wong N, Brunet JS, *et al*: **Germ-line BRCA1 mutation is an adverse prognostic factor in Ashkenazi Jewish women with breast cancer.** *Clin Cancer Res* 1997, **3**:2465–2469.

20. Verhoog LC, Brekelmans CTM, Seynaeve C, *et al*: **Survival and tumour characteristics of breast-cancer patients with germline mutations of BRCA1.** *Lancet* 1998, **351**:316–321.

21. Marcus JN, Watson P, Page DL: **Hereditary breast cancer. Pathobiology, prognosis and BRCA1 and BRCA2 linkage.** *Cancer* 1996, **77**:697–709.

22. Lee JS, Wacholder S, Struewing JP, *et al*: **Survival after breast cancer in Ashkenazi Jewish BRCA1 and BRCA2 mutation carriers.** *J Natl Cancer Inst* 1999, **91**:259–263.

23. Frank TS, Manley SA, Olufunmilayo I, *et al*: **Sequence analysis of BRCA1 and BRCA2: correlations of mutations with family history and ovarian cancer risk.** *J Clin Oncol* 1998, **16**:2417–2425.

24. Chang-Claude J, Dong J, Schmidt S, *et al*: **Using gene carrier probability to select high risk families for identifying germline mutations in breast cancer susceptibility genes.** *J Med Genet* 1998, **35**:116–121.

25. Peto J, Collins N, Barfoot R, *et al*: **Prevalence of BRCA1 and BRCA2 gene mutations in patients with early onset breast cancer.** *J Natl Cancer Inst* 1999, **91**:943–949.

26. • Lerman C, Narod S, Schulman K, *et al*: **BRCA1 testing in families with hereditary breast-ovarian cancer: a prospective study of patient decision making and outcomes.** *JAMA* 1996, **275**: 1885–1892.
Explanation of psychosocial aspects of predictive testing for BRCA1/2.

27. Chabner E, Nixon A, Gelman R, *et al*: **Family history and treatment outcomes in young women after breast-conserving surgery and radiation therapy for early-stage breast cancer.** *J Clin Oncol* 1998, **16**:2045–2051.

28. Easton DF, Ford D, Bishop DT, and Breast Cancer Linkage Consortium: **Breast and ovarian cancer incidence in BRCA1-mutation carriers.** *Am J Hum Genet* 1995, **56**:265–271.

29. Tabár L, Larsson LG, Anderson I, *et al*: **Breast-cancer screening with mamography in women aged 40-49 years.** *Int J Cancer* 1996, **68**: 693–699.

30. Dickersin K: **Breast screening inwomen aged 40–49 years: what next?** *Lancet* 1999, **353**:1896–1897.

31. Lalloo F, Boggis CRM, Evans DGR, *et al*: **Screening by mammography, women with a family history of breast cancer.** *Eur J Cancer* 1998, **34**:937–940.

32. Möller P, Maehle L, Heimdal K, *et al*: **Prospective findings in breast cancer kindreds: annual incidence rates according to age, stage at diagnosis, mean sojourn time, and incidence rates for contralateral cancer.** *Breast* 1998, **7**:55–59.

33. Kollias J, Sibbering DM, Blamey RW, *et al*: **Screening women aged less than 50 years with a family history of breast cancer.** *Eur J Cancer* 1998, **34**:878–883.

34. Forrest APM: *Breast Cancer Screening: Report to the Health Ministers of England, Wales, Scotland and Northern Ireland*. London: HMSO, 1986.

Authors' address: North West Regional Genetics Service, St. Mary's Hospital, and Family History Clinic, Centre for Cancer Epidemiology, Christie Hospital, Manchester, UK

Correspondence: Dr D Gareth R Evans, MD FRCP, North West Regional Genetics Service, St. Mary's Hospital, Hathersage Road, Manchester M13 0JH, UK