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A REVIEW ON PATHOLOGICAL AND MORPHOLOGICAL DIAGNOSIS OF FAMILIAL BREAST CANCER

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Abstract

Approximately 5% of breast cancers are due to a heritable predisposition. This predisposition is due to one of the high risk breast cancer genes BRCA1 & BRCA2. A further proportion of cases arise as familial breast cancer, in the presence of a less striking family history. The morphological features of BRCA1&BRCA2 genes differ from each other & from sporadic breast cancers. Patients with BRCA1 mutations shows as excess of medullary a typical medullary carcinoma. However, multifactorial analysis shows that BRCA1 mutations have a high mitotic count, pushing tumour margins& lymphocytic infiltrate. But patients with BRCA2 mutations show an association with tubular /lobular carcinoma, but not sustantiable in a large ***Breast Cancer Linkage Consortium*** *study. BRCA2 mutations in multifactorial analysis show pushing of tumor margins only. This recent finding of pathological aspects of BRCA1 & BRCA2 means that in addition to bilaterality & family history, a pathological element can enter into the risk calculation for the presence of BRCA1/BRCA2 mutations. This pathological & morphological analysis will facilitate the mutation testing to families with positive result & subsequently implications for clinical management of these families.*

KEY WORDS: *BRCA1, BRCA2, familial, pathology genetic testing.*

INTRODUCTION:

Breast cancer is the commonest malignancy among developed countries women. Approximately one in 12 women will develop breast cancer in their life time. Approximately 95% of breast cancers are sporadic. But 5% of cancers diagnosed in young women, are due to highly penetrant autosomal dominant trait. The models of breast cancer development are based on morphological studies. These studies suggest the transition from a normal epithelial cell via hyperplasia &atypical hyperplasia to ductal carcinoma insitu (DCIS). These studies

were supported by analogy with mouse mammary tumour models & by epidemiological studies, which showed that the risk for breast cancer increased with the rate of proliferation and atypical in breast biopsies. During the past 15 years a number of genes have been identified, which inherited in a mutant form, which offer a high lifetime risk for breast cancer and form a spectrum to other cancers. The most common genes found in the young cancer patients are BRCA1& BRCA2. BRCA1 was mapped to chromosome 17q in 1990 and genetic sequence was published in 1994. [Johnson et al. 2022, Green et al, 2016, Miki et al, 1994].

And then the major localized susceptibility gene BRCA2 was cloned in 1995 on chromosome 13q [Lukong, 2017, Wooster et al, 1994]. Other recently discovered genes that increase the risk of breast cancer are associated with bilateral beginning and malignant breast disease are Cowden's disease which is due to mutations in the PTEN gene[Johnson et al. 2022, Marsh et al,1998] and Peutz-jehger syndrome (PJS) which is due to mutations in CDNK4 [Hemminki et al, 2001]. The life time risk of breast cancer because of these genes is less than 35%.

The histopathological classification of breast cancer is subjective, despite of an attempt to provide clear guidelines [Sloane JP, Ellman R, Anderson TJ, et al, 1975]. No clear agreement has emerged because of the subjective nature of histological examination.a strong association with familial risk has been seen in a histological review of the population based series of 4071 breast cancer in women between the ages of 20 & 54 yrs in the cancer & steroids hormone study [Johnson et al. 2022, Jacobs et al,1999].

The pathologists have tried to identify the morphological phenotypes for localization of breast cancer predisposition genes BRCA1 & BRCA2.

PATHOLOGY OF BREAST CANCER GENE BRCA 1: Breast cancer arising in patients with BRCA1 mutations are of higher grade than sporadic cancer. This statement is supported by a number of reports in the literature [Bignon et al 1995]. Studies of BRCA1 associated tumours from 14 families and their effects in comparision with sporadic breast carcinomas was studied by Eisenger et al. [Lukong, 2017, Eisinger et al, 1996] The first large series of the pathology of BRCA1 related tumours was reported by Marcus et al [Johnson et al. 2022, Marcus et al, 1996] These studies shows the assignment of breast cancer patients to the BRCA1 group on the basis of ovarian and male breast cancer [Hall et al,2003]. The analysis of tumour for histological type, grade, and ploidy and S phase fractions was done. These analysis shows that BRCA1 associated tumours were more likely to be of medullary or

atypical medullary type, and more frequently were aneuploid and had higher tumour cell proliferation rate.

The pathology of the tumour related to BRCA1 were examined and compared with control individuals who did not have a family history of the disease by Breast Cancer Linkage Consortium[Rakha 2022, Lancet, 2004]But this histopathological classification of breast cancer is subjective &an attempt was made to provide clear guidelines for variability[Sloane et al,2003].But the cancers were typed &graded using the criteria used by the UK National Screening Programme . They were graded by giving a score of 1-3 for each parameter. If more than 75% of the tumour has good tubules, the score is 1, if less than 10% of the tumour has good tubules, the score is 3. For pleomorphism the greater the degree of pleomorphism, the worse the score and similarly the higher the mitotic count per10 high power fields, the higher the score. Total scores of 3-5, 6-7 & 8-9 mean that the tumour is of grades I, II&III respectively.

This histopathological result shows no differences between BRCA 1 & control breast cancers, in the proportions of the invasive ductal carcinoma of on special types. More carcinomas were recorded as medullary or atypical medullary in the BRCA 1 group (14%) then in the control group (2%). This is reported by Marus et.al [Green et al, 2016, Marcus et al, 1996]. BRCA, breast cancers are significantly higher than that in the control population breast cancers [Lancet 2003, Lakhani et al, 1998] because of the strong associations of the medullary & atypical medullary carcinoma with the BRCA, phenotype, a further review to identify the features that were predictive for BRCA, phenotype was carried out[Palacios et al, 2008]. Medullary carcinoma is a controversial entity which is defined as a tumor that grows in solid sheets with in an indistinct cell bordes (syncytial growth pattern), has large vesicular nuclei, and prominent nucleoli, abroad pushing margin and a prominent lymphocytic in filtrate both at the periphery and with in the tumour. These features must be present in the entire tumour for it to be regarded as a classical medullary carcinoma [Rakha 2022, Sheffield 1995]. If the tumor has less lymphocytic infiltrate or a infiltrating margin in part of the tumour, it is regarded as an atypical medullary carcinoma. The presence of a classical ductal carcinoma of no special type forming less than 25% of the tumour also pushes it into an atypical medullary carcinoma category. In a multifactorial analysis, the only factors found to be significant were total mitotic count, continuous pushing margins and lymphocytic infiltrate [Green et al, 2016, Ridolfi et al, 1977].

In this multifactorial analysis there is no significant diagnosis of medullary & atypical medullary carcinoma. The 3 features that are independently associated with cancers from the BRCA-1 patient with continuous pushing margins& lymphocytic infiltrates are part of the subset of the characteristics that define medullary carcinoma. High mitotic count is the 3rd feature associated with these tumors, is often seen in medullary carcinomas, this leads to an increase in the frequency of classical & atypical medullary carcinoma which is observed BRCA1phenotype.

PATHOLOGY OF BREAST CANCER GENE BRCA2: The pathology of tumour associated with BRCA2 is limited. [Johnson et al, 2022, Marcus et al 1996, Jensen 2003] attempted to delineate the pathology of BRCA2 tumour. The author suggested that tumours arising in patients with BRCA2 mutations were different from those arising in patients with BRCA1 mutations. These tumours were off lower grade then BRCA1 tumours, were less aneuploid and did not have the high proliferation. They found an association of BRCA2 tumors with invasive lobular carcinoma, tubular-lobular carcinoma, tubular carcinoma and cribriform carcinoma. This in contrast to the finding of Agnarsson et; al. [Rakha 2022, Agnarsson et al, 1998, Rosai 1991], who found that BRCA2 tumours in the Icelandic population who where of higher grade than that of sporadic cases. This data is based only on BRCA2 mutations. These studies show that BRCA2 mutation carriers had no tubular carcinoma, when compared with 5% of the control population. This also shows no evidence of medullary or atypical medullary carcinoma in the BRCA2 group [Johnson et al, 2022, Porter DE, Cohen BB et al 1994]. BRCA2 breast cancers where of higher grade then those from the control population. In contrast to BRCA1, the higher grade of BRCA2 tumours was only due to higher score for tubule formation.

The pleomorphism or mitotic count between BRCA2 tumours and sporadic cancers were same. There was no difference in the incidence of ductal carcinoma insitu between BRCA2 group and control cancers. In BRCA2 mutations lobular carcinoma insitu where seen less frequently than in control individuals.

Multifractional analysis for the BRCA2 mutation carriers [Green et al, 2016, Palacios.J, Robles Frias M.J et al 2008] showed that only significant features were tubule score and continuous pushing margins.

GENETIC TESTING: A number of groups have reports on the likelihood of BRCA1 and to a lesser extent BRCA2 mutation with different family histories. The chances of BRCA1 mutation in individuals with sporadic breast cancer who is under 50 years is less[Peto J,

Collins N et al 1999 Khan SA, Baird C et al 2002, Curtis et al, 2012,], and this would alter significantly if medullary features with family history of breast or ovarian cancer. Most genetic testing is requiring for unaffected women about the risk of breast cancer whose relatives are relevant.

Histology report with medullary features or that all the breast cancers in the family were oestrogen receptor negative and grade would heighten the chance of finding a mutation in family thus enabling the individual to manage the risk. Even if the women does not want to know her own BRCA1/BRCA2 status [Rakha 2022, Curtis et al, 2012, Lerman C, Narod S et al 1999], she may still want to take advantage of ovarian scanning because she would be at half risk for ovarian cancer.

BREAST CANCER MANAGEMENT: Once breast develops in an individual, appropriate management of that cancer is the primary consideration [Wolff 2017]. Because many of these patients are young and have early cancers, breast conservation is in many cases. Wide local excision and axillary node sampling with adjuvant radiotherapy will produce equivalent results to simple mastectomy. For women with either a proved or suspected genetic susceptibility, the chance of recurrence must take into account the background susceptibility of the remaining breast tissue because familial cancers are more likely to be multifocal and bilateral [Rakha 2022]. There is very little data on the conservative management of BRCA1/BRCA2 mutation carriers when compared with those with sporadic disease. At present there is no clear contradiction to breast conservation for the affected breast.

SCREENING FOR BREAST CANCER: Screening by mammography has been accepted in UK for women over the age of 50 years .[Johnson et al, 2022, Forrest APM,1986] A number of studies [Rakha 2022, Lalloo and Boggis 1998,Clin Oncol J 2001]suggest that screening women with a family history of breast or ovarian cancer is of use. If a women 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 BRCA1 mutation. Unaffected women in this type family of should be offered mammography screening. Because tumour associated with BRCA1 mutation are highly proliferative. The pathology of breast cancers can therefore be used for direct clinical screening of families as well as genetic screening.

OTHER STUDIES: In the feature the following studies should be under taken to clarify 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.
4) The inclusion of pathology data into the risk evaluation equation in families already tested for BRCA1 / BRCA2 mutations.

CONCLUSION: The studies indicate that breast tumours arising in patients with BRCA1 mutations are different from those arising in patients with BRCA2 mutations and from non-familial cancers. The principle difference is in total mitotic count, lymphocytic infiltrate, tubule formation. Patients with BRCA2 show high rate of male breast cancers and lower incidence of ovarian cancer. The differences in the clinical phenotypes associated with mutation in the two genes suggested that the biological activities of the proteins encoded by the BRCA1 and BRCA2 are different. The pathology of their breast cancer gives further information in deciding which sample represents a high priority for genetic testing.

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