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Role of BRCA1 in Diagnosis of Triple Negative Breast Cancer

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Abstract

Triple-negative (TN) tumors are considered to be the most common subtype breast cancer in individual who carry BRCA1 mutation. in the recent years BRCA1 testing was advised to be offered to all individuals who are below 50 years and whom carry Triple negative breast cancer. Furthermore BRCA1 mutation frequency and the amplification for clinical practice of undertaking genetic testing in women with TN breast cancer have been evaluated.

Introduction

Breast cancer is a type of cancer that starts in the breast, when cells begin to grow out of control, and Breast cancer cells usually form a tumor that can often be seen on an x-ray or felt as a lump. Breast cancer occurs almost entirely in women, but men can get breast cancer, too. TNBC (Triple Negative Breast Cancer) is cancer that tests negative for three hormones receptors, estrogen receptors, progesterone receptors, and have little or no HER2 protein expression.[5,6]

The lacking of expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor (HER2) describe the TNBC (Triple Negative Breast Cancer) which is a subgroup of tumors[1] , However, TNBC (Triple Negative Breast Cancer) are a collection of different breast cancers that are still poorly characterized at the molecular level, and lack definitive prognostic markers and selective targets of therapy[2]. Although its incidence is still high, the overall mortality due to breast cancer has decreased, in addition, it accounts for about 15% of all breast cancers, and it occurs more in younger women than the older ones and it occurs more frequently in individuals with a germline BRCA1 mutation.[3]

The relationship between BRCA1 gene and breast cancer is that the gene is a tumor suppressor gene that contributes to repair of damaged replication forks and double-strand breaks, transcriptional regulation in response to DNA damage, chromatin remodeling, and regulation of cell division, apoptosis, and transcription, When cells lacking functional BRCA1 or BRCA2 are deficient for double-stranded break repair, resulting in genomic instability that leads to cancer predisposition.[4]

The identification of a BRCA mutation has profound crucial consequences for clinical management impacting on the possibility of developing contralateral breast cancer and/or ovarian cancer and increasingly having implications for optimal therapy. but due to financial and logistical constraints, BRCA testing is currently rationed in most countries. BRCA testing is typically undertaken In the united states and much of Europe, if the likelihood of detecting a mutation is about 41% , also in the UK. The National Institute for Health and Clinical Excellence (NICE) recommended that if the possibility of finding a mutation is about 42%, therefore testing should minimally be offered, irregardless many UK centers also offer testing if the likelihood is between 10 –20%.[(1)]

Several different methods are used in clinical practice to determine which cases are qualifiable for testing are utilized in clinical practice, specialized knowledge and/or software are required in most of them. the strong association between the TN phenotype and BRCA1 mutations has led to the association of efforts for establishing the frequency of BRCA1 mutations in individuals with TN breast cancer. Till nowadays, alot of small studies have evaluated this in both unselected series and case series selected on the basis of family history and/or age(Table 1). [(1)]

The **aim** of this study is to prove that TNBC (Triple Negative Breast Cancer) occurs more in individuals who carry BRCA1 germline mutation or have family history or they are below 50 years.

Materials & Methods

308 individuals with TN breast cancer were undertaken BRCA1 mutation analysis, these individuals were divided into two groups, the first group includes 159 individuals from unselected series whereas the second group includes 149 individuals from series ascertained on the basis of young age and/or family history, and it is considered to be the largest study to date. the data had used by them to further evaluate the mutation frequency and to consider the practical ramifications of undertaking BRCA testing in individuals with TN breast cancer**.[(1)]**

BRCA1 analysis

This is done by multiplex ligation-dependent probe amplification (MLPA) analysis for large deletions/duplications, was performed in DNA from all cases.[1]

Age-specific TN breast cancer incidence

National breast cancer figures are not subclassified the status by receptors in England. Therefore, they used the national figures for age-specific breast cancer incidence which is published by the Office for National Statistics for England to be estimated annually, and data from a study of 159 cases of breast cancer subtyped by immunohistochemistry. This allowed them to estimate the annual age-specific incidence of TN breast cancer in England.**(1)**

Eligibility for clinical BRCA testing

Family history data was available in 271 individuals, which included 122 out of 159 individuals in the unselected series and all individuals in the selected series. they used these data to calculate the Manchester score for each family to evaluate whether the individual would be eligible for clinical BRCA testing (Table2). Overall, approximately a third of cases (85 out of 271; 31%) were eligible for clinical BRCA gene testing, though as expected this was lower in the unselected series (20 out of 122; 16%), particularly at older ages (Supplementary Table 1). If one considers the individuals with BRCA1 mutations for whom they could calculate the Manchester score, 15 out of 42 (36%) were not eligible for clinical BRCA testing**.(1)**

Results

The full results of all 308 cases which are given in Supplementary (Table1). in 308 individuals there was about 45 BRCA1 mutation (14.6%). This included 15 (9.4%) BRCA1 mutations in 159 individuals in the unselected series, and 30(20.1%) BRCA1 mutations in 149 individuals in the selected series (Table 2). In individuals who aged over 50 years in both the unselected and selected series there was a strong age effect with marked decrease in mutation frequency (Table 2). If one considers just individuals with sporadic TN breast cancer, that is, those without a first or second degree relative with breast or ovarian cancer, 8 out of 103 (8%) had a BRCA1 mutation, and all were under 50 years of age.

Table 1 studies with over 50 cases that have evaluated BRCA1 mutation prevalence in TN cancers.[(1)]

Number of cases	**BRCA1 mutation(%)**	**Unselected/Selected**	**Selection criteria**
144	14	Unselected	
96	9	Selected	Bilateral and/or family history of breast cancer. Seen in genetic clinic and underwent BRCA testing.
93	34	Selected	
77	16	Unselected	
64	30	Selected	Tested for founder mutation.
63	13	Selected and unselected	TN below 41 years.
54	9	Selected	TN below 41 years and did not qualify for testing.

Table 2 summary of BRCA1 mutations in 308 TN breast cancer cases.[(1)]

	Unselected series BRCA1 mutation/all(%)	**Selected series BRCA1 mutation/all(%)**	**Total BRCA1 mutation/all(%)**
All	15/159 (9)	30/149 (20)	45/308 (15)
Below 50 years	11/58 (19)	26/111 (23)	37/169 (22)
Over 50 years	4/101 (4)	4/38 (11)	8/139 (6)

Discussion

Triple-negative breast cancer (TNBC) is a subtype of aggressive breast cancer and characterized by a lack of the expression of estrogen receptor, progesterone receptor and human epidermal growth factor receptor 2. When the BRCA genes are mutated, they cause the defectibility of DNA repair mechanism, the latter increases the risk of developing breast and/or ovarian cancer.[4,5]

In this study, They have undertaken the largest analysis of BRCA1 in TN breast cancer to date, and showed that the frequency of BRCA1 mutations in unselected individuals with TN breast cancer is about 10%, increasing to about 19% in individuals who diagnosed below 50 years. The latter is similar to the frequency of BRCA1 mutations (23%) in individuals diagnosed before 50 years that were selected for inclusion because of a family history of breast cancer and/or young age at diagnosis.[1]

This study included samples and figures which would be obtainable from larger, prospective studies. Nevertheless, their results are similar to those previously reported and they believe that they are likely to be broadly accurate (Table 1). they estimated the proportion of individuals included in this study that would currently qualify for a clinical BRCA test. their analysis suggests that over a third of the BRCA1 mutation positive individuals they identified would not have been eligible for clinical genetic testing in departments that use a 10% mutation detection threshold.[1,2]

Additionally, studies to define testing criteria in individuals who are not eligible for testing using current systems (e.g., individuals with TN breast cancer but without a family history) have been undertaken. they believe a drawback to these approaches is that complex evaluation by specialist practitioners is typically required for most cases, but is unnecessary in the sizeable proportion eligible for testing on the basis of age alone.A simpler approach, which would be readily comprehensible by clinicians and patients, would be to define a BRCA testing eligibility criteria for women with TN breast cancer based on age. However, implementation of routine BRCA testing in all TN breast cancers diagnosed before 50 years would increase the logistical and financial burdens on genetic departments.[1]

They estimate that it would lead to about 1200 extra tests in England each year, which may be challenging for some departments to immediately implement with current resources and procedures. However, new sequencing technologies are leading us into an era of fast, affordable gene testing. Together with procedural reorganisation to allow BRCA testing in affected individuals to be undertaken though oncology services, this should enable genetic services to introduce BRCA testing to women with TN breast cancer diagnosed below 50 years of age, within the next few years.[1]

Conclusion

In conclusion women, who are below 50 years with TN breast cancer have more than 10% of likelihood of carry BRCA1 mutation and therefore they are capable of being tested in most centers. however, short term logistical and financial burdens on genetic service maybe placed by implementation. Further research and test should take place in the near future.

References

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