Retrospective Analysis of Breast Cancer Patient Data for Identification of Candidates for BRCA Mutation Detection

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Introduction: Breast cancer is the leading type of cancer affecting women, with an increasing trend of mortality, and a lifetime risk of more than 10%. There are cases of inherited predisposition, which is mostly caused by mutations of the tumor suppressor genes BRCA1 and BRCA2. The objective of this retrospective study is to identify presumptive candidates for BRCA1 mutation carriers using available clinical, histopathological and immunohistochemical data.

Material and method: We processed the available recorded data of 1334 patients diagnosed with breast cancer between the years 2005 and 2010 from the archives of the Pathology Department of the Clinical County Hospital Tg.-Mures. We considered age under 45, histopathological characterization and available immunohistochemical information.

Results: The main selection criteria (age below or equal to 45 years) excluded the majority from further analysis, while 188 cases (12.35%) remained. After performing distribution into histopathological type groups, we looked at the immunohistochemical data. We obtained 19 ER-/PR- negative cases without Her2/neu information, and only 12 cases could be proven to be triple negative, and thus to be considered as primary candidates for BRCA mutation screening.

Conclusions: We identified a very small number of presumptive BRCA mutation carrier candidates. This is due mostly to the fact that the information available comprised macroscopic and classical histopathological data. Immunohistochemical characterization is not widespread, but this shortcoming will be circumvented by prospective reprocessing of the archived biological materials, in order to characterize the BRCA mutation patterns of our population.

Keywords: BRCA mutation, breast cancer, patient selection

Introduction

Breast cancer is the leading type of cancer affecting women, with an increasing trend of mortality, and a lifetime risk of more than 10%. At a global level it comprises 23% of all cancers of females [1]. In Romania, breast cancer is also the primary cancer of women, with an age standardized rate (ASR) of incidence of 45.4/100,000 people, and an ASR of mortality of 15.6/100,000 people [2]. Ovarian cancer displays a lower frequency, and a lower lifetime risk of 1.8%.

This however refers to all types of breast and ovarian cancers sporadic and familial alike. There is a special situation in case of inherited predisposition, which is mostly caused by mutations of the tumor suppressor genes BRCA1 and BRCA2. Although there is controversy concerning the true scale of risk, women with mutations in these genes are significantly more susceptible to develop breast and/or ovarian cancer than the general population [3]. Lifetime risk of breast cancer is around 90% for both mutations. In case of BRCA1, by the age of 50 years 45% of mutation carriers have developed the disease.

The objective of this retrospective study is to identify presumptive candidates for BRCA1 mutation carriers using available clinical, histopathological and immunohistochemical data.

Material and method

We processed the available recorded data of 1334 patients diagnosed with breast cancer between the years 2005 and 2010 from the archives of the Pathology Department of the Clinical County Hospital Tg.-Mures. The focus of analysis was age, histopathological type, immunohistochemical status and family history (if available).

Since there was almost no family history available for these patients, we considered only patients below or equal to 45 years of age. Age under 45 at time of diagnosis is considered to be a strong predictive factor for BRCA mutations. After establishment of this subgroup we looked into the histopathological characterization of the included tumors, sorting them into several groups: ductal, lobular, mixed, medullary, other and undetermined. Finally, we recorded the available immunohistochemical information: estrogen and progesterone receptor status, Her2/neu score, and potentially other markers as HMW-CK, Ki67 and p63.

Results

Our study included 1334 breast cancers in a consecutive series of unselected patients diagnosed between 2005 and 2010. The main selection criteria (age below or equal to 45 years) excluded the majority from further analysis, while 188 cases (12.35%) remained in focus.

All of these were females, and there were no male breast cancers diagnosed in this age group. The distribution into histopathological type groups is presented in Table I.

The highest probability for BRCA mutation is characteristic to medullary type, of which we had only one case.

Table I. Histopathological type distribution of the analyzed cases

Histopathological type	No. of cases	Percentage (%)
Ductal	125	66.49
Lobular	17	9.04
Mixed	2	1.06
Medullary	1	0.53
Other	16	8.51
Undetermined	27	14.36
Total	188	100

Table II. Available immune status information

n=31	Triple negative	ER-/PR- (no HER2 info)
Ductal	9	14
Lobular	0	0
Mixed	1	2
Medullary	0	0
Other	1	2
Undetermined	1	1
Total	12	19

Ductal type is also frequent in this context, and the majority of cases were of this type.

Unfortunately there was no immune data concerning the single one medullary case. We also noted that Her2/neu status was observed only in a very small number of cases, which makes classification difficult.

As a result we obtained 19 ER-/PR- negative cases without Her2/neu information, and only 12 cases could be proven to be triple negative, and thus to be considered as primary candidates for BRCA mutation screening (Table II).

Discussions

Early detection of BRCA germline mutations is essential for the correct management of these patients. In order to provide the most effective treatment, the therapeutic range needs to be applied individually to each breast cancer patient [4]. There are targeted therapeutic strategies for BRCA-associated breast cancer, and also a more radical surgical approach is recommended in BRCA mutation carrying women with newly diagnosed breast cancer [5].

Presently, BRCA screening is very labor intensive and expensive. There are several accepted criteria and selection algorithms for narrowing the target population who will be recommended for genetic testing. The most widely recommended criteria are the family history of breast and ovarian cancer, and personal history of early breast cancer (<45 years), bilateral breast cancer or simultaneous breast and ovarian cancer. A family history suggesting at least 10% BRCA mutation probability is accepted as a criterion for recommending the patient for genetic testing [6]. It is somewhat difficult to document a detailed family history in the clinical setting, and also the obtained information is mostly reliant on personal stories of the patient and relatives (thus unverified). Also, due to various reasons, in almost 50% of the cases there is no notable family history as far as the disease is concerned.

Further data that can be utilized for screening BRCA mutation candidates comprises histopathological phenotype and more recently IHC characterization of the tumor tissue. As compared to sporadic breast cancer, BRCA mutation associated breast cancers display the following histopathological characteristics: mostly higher grade (G3) and higher proliferation rate, central necrosis and nuclear pleomorphism. The correlations between these characteristics and immunohistochemical features in our patient group are yet to be determined. The majority of BRCA tumors are medullary type, or related subtypes, but there are also invasive ductal carcinomas [7]. The majority of our candidate cases were ductal or intraductal cancers, and one single medullary type.

As far as immunohistochemical classification is concerned, BRCA tumors are predominantly of basal-like subtype, characterized by expression of CK5/6, CK14 and CK17. The most important feature is missing expression of estrogen receptors (ER-), progesterone receptors (PR-) and human epidermal growth factor receptor 2 (Her2/neu-). These cancers are delineated as triple-negative breast cancers [8]. We could identify a limited number of confirmed triple negative cases, mostly because of missing Her2/neu information. This further reduced the number of possible mutation carriers to 12. As there is positive correlation between triple negativity and the ductal histopathological type, presently 9 cases would be recommended for BRCA genetic testing. Naturally, after reprocessing of the archived biological materials, and completion of the missing data, a new and clearer view of the picture will be achieved.

Conclusions

Based on the above mentioned characteristics, we identified a very small number of presumptive BRCA mutation carrier candidates. This is due mostly to the fact that the information available comprised macroscopic and classical histopathological data. Immunohistochemical characterization is not widespread, but this shortcoming will be circumvented by prospective reprocessing of the archived biological materials of these tumors, in order to characterize the BRCA mutation patterns of the population in our geographic area.

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