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CLINICAL TRIAL

Multigene panel testing in unselected Israeli breast cancer cases: mutational spectrum and use of BRCA1/2 mutation prediction algorithms

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Abstract

Background Studies assessing the contribution of non-*BRCA1/2* gene mutations to inherited breast cancer (BC) predisposition consistently reported low (up to 4%) yield. The current study aimed at assessing the spectrum of non-*BRCA* mutations in unselected Israeli BC cases and the utility of BRCAPRO and Penn II models, as tools for prediction of detecting non-*BRCA1/2* mutations in Israeli BC patients who tested negative for the predominant Jewish *BRCA1/2* mutations.

Methods All consecutive Jewish Israeli BC patients at the Sheba Medical center who tested negative for the predominant *BRCA1/2* mutations and elected to perform multigene panel testing were included. For each patient probability of *BRCA* mutation detection was calculated by the Penn II algorithm and the BRCAPRO tool.

Results Overall, 144 cases were included (median age at diagnosis was 48, range 20–73 years); 48% were Ashkenazim. One patient harbored a non-founder *BRCA1* mutation (c.5434C>G; p.P1812A). Pathogenic/likely pathogenic (P/LP) mutations in non-*BRCA1/2* genes were detected in additional 14/144 patients, including *CHEK2* ($n=5$), *RAD51D* ($n=2$), *MSH6* ($n=2$), and one each in *ATM*, *RET*, *TP53*, *NBN*, and *BAP1*. Using a cutoff of 15% probability of *BRCA* mutation detection, both models accurately predicted the observed carrier rate of non-*BRCA* mutations.

Conclusions In unselected Jewish Israeli BC patients, the rate of detecting non-founder *BRCA1/2* mutations is low, with *CHEK2* mutations detected in 3.4% of cases. *BRCA1/2* mutation prediction models may be utilized for selecting patients eligible for further multigene panel testing after exclusion of predominant *BRCA1/2* mutations.

Keywords Breast cancer · Non-BRCA1/2 · Prediction models · Cancer susceptibility genes

Introduction

Genetic testing for cancer susceptibility (oncogenetics testing) is traditionally recommended for patients with a personal and/or family history suggestive of inherited cancer predisposition that may be associated with germline mutations in one of several high-penetrance genes. For breast cancer (BC) cases, expert guidelines define the features suggestive of patients most likely to benefit from oncogenetic testing for hereditary cancer syndromes [1–3]. Several risk prediction tools are currently available online, including BRCAPRO [4], Penn II [5], Myriad BRCA Risk calculator [6], BOADICEA [7], Tyrer-Cuzick [8] and others. In addition to the ability of some of these algorithms to assess individual's lifetime risk for developing BC, they also quantify the likelihood of carrying a *BRCA1* or *BRCA2* germline mutation (*BRCA* carrier probability). *BRCA* carrier probability prediction models take into account clinical characteristics such as ethnicity, age at diagnosis of BC or other cancer types in the proband and other family members, and, in some algorithms, histological features of BC. The sensitivity and specificity of these algorithms vary based on their inherent differences and weighted analyses and depending

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on the populations where these tools were generated and validated [9, 10].

The limited spectrum of recurring mutations in *BRCA1/2* in specific populations, notably in Ashkenazi Jews, as well as Icelandic and Polish populations, resulted in a stepwise *BRCA* genotyping strategy for these populations [11]. In Israel, patients are initially tested for the predominant, recurring mutations in these two genes [12]. Previous studies evaluating the yield of comprehensive analysis of *BRCA1/2* among Ashkenazi (AJ) and non-Ashkenazi (NAJ) Jewish high-risk individuals, reported rates of non-founder mutations below 5% [10, 13]. Furthermore, studies assessing genetic predisposition for cancer that may be attributed to non-*BRCA1/2* gene mutations in unselected BC patients of diverse ethnicity have consistently reported 3–4% yield of such testing [14, 15].

The decreasing costs of next-generation sequencing (NGS)-based multigene panels, which simultaneously test for multiple genetic conditions, enable overcoming phenotypic heterogeneity seen in various clinical scenarios. A few studies suggested that common hereditary cancer syndromes, like Lynch and hereditary breast and ovarian cancer (HBOC) syndromes, may have some phenotypic overlap [16, 17]. This may suggest that the above-mentioned algorithms for assessment of an individual's risk for carrying *BRCA1* or *BRCA2* germline mutation, may also be used to evaluate risk for carrying non-*BRCA* mutations. This notion was raised by Berry and coworkers even before NGS-based panels became available [18]. Although in some countries these multigene panel tests are available, accessible, and are becoming more affordable, in other countries, health-care systems regulators define specific subsets of patients for which testing should be considered, offered, and covered by health insurers. These restrictions stem from a combination of limited resources (either shortage of genetic counseling services or lack of reimbursement), undetermined clinical utility in low-risk populations, and unclear clinical actionability of some of the genes with low-moderate penetrance [2, 3, 19]. Thus, the aims of the current study were to evaluate the rate and spectrum of mutations in an extended multigene panel testing in unselected Israeli BC cases who tested negative for predominant *BRCA1/2* mutations and assess the utility of *BRCA1/2* carrier prediction algorithms as a tool for selection of patients for second step genotyping of *BRCA* and non-*BRCA* gene mutations.

Patients and methods

Study population

The study included individuals referred for oncogenetic counseling at the Oncogenetic services at the Sheba Medical Center, Tel-Hashomer, From April 2013 to December 2018. All had a personal history of BC, or personal BC with additional cancer types. Family history of cancer was not used as a selection criterion. All study participants tested negative for predominant Israeli *BRCA1/2* mutations prior to performing multigene panel testing. All patients performed multigene testing upon their request, since this testing is currently not reimbursed in Israel and is paid by the patients. Detailed personal and family history of cancer were collected during genetic counselling. Self-reported ethnicity was defined by place of birth of the parental and maternal grandparents. The study was approved by the IRB, and each patient signed an informed consent.

Calculation of *BRCA1/2* mutation probability

For each patient, *BRCA* mutation probability was calculated by the Penn II online tool (https://pennmodel2.pmacs.upenn.edu/penn2/) and a simplified, less time-consuming, version of BRCAPRO tool, freely available through HughesRiskApps (HRA; http://www.HughesRiskApps.net). Since none of the models incorporates exclusion of predominant *BRCA1/2* mutations, the risk assessment was based on the prior-to-testing clinical data. In the ethnicity field of the BRCAPRO model questioning "Grandparents of Jewish descent", for Ashkenazim the answer was "yes", for Non-Ashkenazi or mixed Ashkenazi Jews—"not sure".

Genotyping

Several CLIA-certified commercial laboratories were used for multigene germline testing, based on patients' preferences and availability of shipping services of the samples to the specific laboratories. These included Counsyl 36-gene panel [20], InVitae 83-gene panel [21], or Color Genomics 30-gene panel (described at https://s3.amazonaws.com/color-static-prod/pdfs/validationWhitePaper.pdf).

Statistics

The calculated median and average scores were compared between the subgroups of patients with positive (pathogenic or likely pathogenic (P/LP) mutation detected) and negative [including variants of uncertain significance (VUS)] results using a Student's *t* test.

Results

A total of 144 BC patients (1 male) were analyzed in the current study. Median age of diagnosis was 48 years (range 20–73). Sixty-nine (48%) were full AJ (all 4 grandparents reported AJ), and 68 (47%) were NAJ. The rest ($n=7$) were

of mixed AJ and NAJ ethnic origin. Notably, only 7 patients underwent comprehensive *BRCA1/2* sequencing prior to performing multigene panel testing. P/LP mutations were detected in 15 patients (10.3%). Demographic data of the study participants and average/median probabilities of carrying *BRCA1/2* mutations calculated by both models are shown in Table 1.

Table 2 summarizes the list of detected mutations using the multigene panels, number of patients with each mutation and the calculated *BRCA* carrier probabilities by both models. Seven cases (4.9%) carried the c.3920T>A; p.Ile1307Lys (rs1801155) variant in the *APC* gene (one of them was a homozygous carrier) and were considered "negative" for the purposes of the current analysis (as this variant has never been consistently shown to be associated with BC risk [22]). Only one patient harbored a non-founder *BRCA1* mutation c.5434C>G; p.Pro1812Ala (rs1800751). Five additional patients were found to carry a *CHEK2* mutation: 3 harbored the common Ashkenazi c.1283C>T; p.Ser428Phe (rs137853011) variant, considered a pathogenic, low-penetrance variant. Neither of the two patients with *MSH6* mutations fulfilled the Bethesda or Amsterdam II criteria for Lynch syndrome. The patient who carried the c.434T>A, p.Leu145Gln (rs587782197) *TP53* mutation fulfilled Chompret criteria for Li-Fraumeni syndrome [23]. Although initially this variant was assigned as variant

Table 1 Demographic data and calculated probabilities of carrying *BRCA1/2* mutations

	All	Positive panel (excluding *APC* I1307K)	Negative/VUS panel[a]	*p* value
Number of pts	144	15	74/55	
(Female/male)	(143/1)			
Age, median (range)	48	41 (28–70)	49 (20–73)	
Full Ashkenazi	69	9	60	
Mixed Ashkenazi	7	1	6	
Sephardi	68	5	63	
Median Penn II probability (range)		20% (4–47)	14% (3–58)	
Median BRCAPRO probability (range)		28% (0.6–75)	11.4% (0.3–97)	
Mean Penn II probability		20.70% ± 10.9 SD	16.50% ± 10.3 SD	0.1393
Mean BRCAPRO probability		32.50% ± 22.3 SD	21.70% ± 23.7 SD	0.095

VUS variants of unknown significance

[a]Including patients with *APC* I1307K variant

Table 2 List of detected variants

Mutation	No. of pts with detected mutation	BRCAPRO probability (%)	Penn II probability (%)
ATM c.1027_1030delGAAA; p.Glu343Ilefs (rs587780612)	1	71	21
CHEK2 c.499G>A; p.Gly167Arg (rs72552322)	1	25	16
CHEK2 c.1283C>T; p.S428F (rs137853011)	3	20, 28, 28	23, 31, 47
CHEK2 c.846+1G>C (rs864622149)	1	42	20
RET c.1998G>C; p.Lys666Asn (rs146646971)	1	75	30
MSH6 c.3743_3744insT; p.Tyr1249Leufs (rs786201084)	1	8.3	11
MSH6 c.3959_3962delCAAG; p.Ala1320Glufs (rs267608120)	1	17.8	11
BRCA1 c.5434C>G; p.P1812A (rs1800751)	1	40	9
RAD51D c.556C>T; p.Arg186* rs387906843	2	28, 65	24, 31
NBN c.966C>G; p.Tyr322* (not reported)	1	0.6	4
TP53 c.434T>A; p.Leu145Gln (rs587782197)	1	24	17
BAP1 c.783+2T>C (rs774730309)	1	15.3	16
APC c.3920T>A; p. Ile1307Lys (rs1801155)	*7*	*5.3–70*	*14–46*

of unknown significance (VUS), it was re-classified as LP based on detailed family history data provided by us. Interestingly, two unrelated AJ patients carried an identical mutation in the *RAD51D* gene—c.556C>T; p.Arg186Ter (rs387906843).

Table 3 shows *BRCA* carrier probabilities by both Penn II and BRCAPRO models and the observed findings. At the cutoff of 15% probability of *BRCA* mutation detection, both models had similar predictive value, with two more patients "missed" by Penn II model compared with the BRCAPRO tool: one *BRCA1* and the other *MSH6* mutation carriers. Raising the cutoff above 20% would yield the same proportion of carriers detected, however, missing more carriers—7/15 by Penn II model and 5/15 by BRCAPRO.

Discussion

In the present study, the spectrum and rates of detected mutations were not significantly different from those previously reported in studies accessing non-*BRCA* mutations in unselected BC patients and Israeli high-risk individuals by multigene panels [14, 15, 24]. Thus, it seems that these low rates of private, non-founder *BRCA* mutations as well as the ability to genotypically define the molecular basis of inherited predisposition to BC when extending the genotyping platform to additional genes should be communicated to the counseled individuals. In addition, the ability to find mutations in actionable genes, affecting the subsequent clinical recommendations should also be considered in the course of the pretest counselling. Notably, in the current study the *MSH6* gene mutations were incidental and unexpected. Additionally, should a 41-year woman with BC who carries a pathogenic *RET* gene mutation be offered prophylactic thyroidectomy is still unresolved.

To the best of our knowledge, this is the first study to show that setting a cutoff of 15% for *BRCA* carrier probability using two different algorithms may be utilized for accurate decision-making when selecting BC patients most likely to benefit from multigene panel testing after excluding the predominant Jewish mutations in *BRCA1/2* genes. The traditional methods of genetic counselling and testing in most countries are regulated by the health insurers and the HMO's or government agencies and primarily rely on specific personal and family history criteria in order to identify patients eligible for oncogenetic testing [19]. Yet, these criteria apply only for *BRCA1/2* testing in BC or ovarian cancer (OC) cases [19], but not for other cancer susceptibility genes. For some of the high-penetrance genes, especially those associated with distinct inherited cancer syndromes (e.g., *TP53*, *PTEN)*, specific diagnostic criteria have been developed [25], but for most other non-syndromic cancer predisposing conditions, no testing criteria exist. These include a few actionable, moderate-penetrance genes, such as *RAD51C/D*, *PALB2*, *ATM* [25], which may explain a subset of familial breast, ovarian, pancreatic or prostate cancers. Additionally, some of these genes are related to homologous repair (HR) pathway and are currently being investigated as a biomarker for efficacy of PARP-inhibitors, after showing intriguing results in advanced prostate cancer patients carrying germline mutations in HR repair pathway-associated genes [26].

Discussing the clinical utility of prediction models for genotyping selection may seem unnecessary considering studies suggesting cost-effectiveness of population-based panel testing for high- and moderate-penetrance OC/BC gene mutations in unselected average risk women [27]. This follows earlier prospective studies that have clearly shown that population-based founder mutation-based *BRCA1/BRCA2* testing in AJ is feasible, acceptable, and highly cost-effective [28–30], Furthermore, applying clinical criteria for selecting individuals who should be offered oncogenetic testing in the AJ population may miss about 50% of asymptomatic carriers [28, 29, 31]. However, extending population-based oncogenetic testing to populations with low rates or non-existent founder mutations

Table 3 Probabilities of *BRCA1/2* mutation detection and observed findings

Mutation probability	Number of patients	No. of patients with positive panel[a]	Missed mutations (no. of patients)
Penn II < 10%	39	2 (5%)	
BRCAPRO < 10%	63	2 (3.2%)	
Penn II < 15%	76	4 (5.3%)	
BRCAPRO < 15%	74	2 (2.7%)	
Penn II ≥ 15%	68	11 (16%)	NBN (1), BRCA1 (1), MSH6 (2)
BRCAPRO ≥ 15%	70	13 (18.6%)	NBN (1), MSH6 (1)
Penn II ≥ 20%	46	8 (17%)	NBN (1), BRCA1 (1), MSH6 (2), BAP1 (1), CHEK2 (1), TP53 (1)
BRCAPRO ≥ 20%	60	10 (16.7%)	NBN (1), MSH6 (2), CHEK2 (1), BAP1 (1)

[a]Excluding patients with *APC* I1307K variant

might pose considerable financial burden, ethical and other barriers (thoroughly discussed by Foulkes et al [19]), irrespective of the decreasing costs of genotyping techniques. Although some geneticists predict that in the near future WGS/WES will be integrated into routine health-care [19], until health-care systems are ready to utilize these genotyping platforms, a rational, evidence-based approach to oncogenetic testing in cancer patients is still warranted in most countries where medical care is not privately-funded.

There are several limitations to the current study. The number of participants is small, with statistically non-significant differences between the calculated mean probabilities of the patients with positive and negative panel results. However, it encompasses patients ranging from very low familial cancer risk to cases with extensive family histories, highly suggestive of cancer susceptibility. Additionally, our results suggestive of specific cutoffs for better prediction of mutation probabilities may not be applicable to populations where founder mutations do not exist. Lastly, BOADICEA model, which predicts mutations in three of non-*BRCA1/2* genes (*PALB2*, *CHEK2* and *ATM*), was not used in our analysis. This is mostly because of time-consuming data entry relating to family history. It is possible that this model would yield different results.

It is an intriguing finding of an identical *RAD51D* mutation in two seemingly unrelated patients in such a small cohort, both from AJ ancestry. However, since in a large cohort of AJ women with a primary diagnosis of invasive BC from the New York Breast Cancer Study (NYBCS), tested by BROCA panel of 23 breast cancer predisposition genes including *RAD51D*, no carriers of this specific mutation were reported [14], our result probably reflect a coincidence or an unknown familial relationship.

In conclusion, our analysis of a small cohort of unselected for family history Jewish Israeli BC patients suggests that the rate of mutations detected in other cancer sensibility genes is low, incidental findings in high penetrance genes unrelated to personal or family history of cancer should be discussed pretesting and that *BRCA1/2* mutation prediction models may be utilized for selection of patients eligible for further oncogenetic testing after exclusion of predominant *BRCA1/2* mutations. Our findings should be examined in a larger cohort, and in other populations where stepwise approach for cancer predisposition testing is utilized. If validated, a different approach for oncogenetic testing may be considered to enable more cost-effective and clinically relevant investigation in BC patients who do not fulfil clinical criteria for specific highly penetrant cancer susceptibility syndromes.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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