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EPIDEMIOLOGY

Inherited predisposition to breast and ovarian cancer in non-Jewish populations in Israel

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Abstract
Purpose The contribution of genetic factors to cancer in non-Jewish populations in Israel is understudied. Yet the early, mostly premenopausal age at breast cancer diagnosis is suggestive of an inherited predisposition.
Methods High-risk cancer cases of non-Jewish origin who were counseled at the Oncogenetics unit, Sheba Medical Center and the oncology institute at the Ziv medical center from January 1, 2000 to December 31 2016 were eligible. DNA extracted from leukocytes was subjected to massive parallel, next-generation sequencing using the Color Genomics platform. Data were analyzed for pathogenic and likely pathogenic mutations using existing pipelines.
Results Overall, 68 cases, each representing a unique high-risk breast/ovarian family, were genotyped: 32 Druze, 26 Muslim Arabs, and 10 Christian Arabs. Fifty-nine had breast cancer (mean age at diagnosis 42.7 ± 7.6 years), and 9 had ovarian cancer (51.6 ± 9.7 years). Overall three pathogenic mutations one each in *BRCA1, PALB2, and BRIP1* genes were detected mostly in Druze families. In addition, 29 variants of unknown significance were also detected, and in 36 cases no sequence variants were noted in any of the genotyped genes.
Conclusion The contribution of the known cancer susceptibility genes to the burden of inherited breast/ovarian cancer predisposition in non-Jews in Israel is modest. Other genes or molecular mechanisms account for the familial breast/ovarian cancer clustering in this population.

Keywords Inherited cancer · Cancer susceptibility genes · Cancer panel testing · Consanguineous marriage · Isolated populations · Non-Jewish Israeli populations

Introduction

Breast cancer (BC) is the most common female malignancy in developed countries, including Israel. While most BC cases have no discernible family history of cancer, familial clustering of cancer is reported in ~20% of cases, suggestive of the contribution of genetic factors to BC phenotype. Furthermore, in a subset of these familial cases, inherited BC, phenotypically hallmarked by early age at diagnosis, bilateral BC, associated cancers (e.g., ovarian, pancreatic), and an autosomal dominant mode of transmission, is noted [1]. Inherited BC is predominantly associated with germline mutations in the *BRCA1* and *BRCA2* genes detected in ~30% of BC high-risk (HR) families [2, 3]. Mutations in additional genes evaluated as BC predisposition genes (e.g., *PALB2, RAD51C, RAD50*) contribute marginally to the overall burden of familial inherited BC risk in most populations studied [2–4].

In Israel, there are ~4000 new cases of BC diagnosed annually, with the majority in the Jewish population, and

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within the Jewish population the highest rates are among Ashkenazi (East European) Jewish women (http://www.health.gov.il/). While the rates of BC among non-Jewish (mostly Arab and Druze) women in Israel are lower than those for Jewish women, there has been an increase in the rate of BC diagnosis among non-Jewish women in Israel since the 1980s: The age-standardized rate (ASR) for Jewish women was 71.1/100,000 in 1979–1981 and increased by 45.7%–103.6/100,000 in 2000–2002. These rates for non-Jewish women in Israel were 14.1/100,000 and 42.6/100,000, respectively, for the same time period, a threefold increase [5]. Furthermore, the age at diagnosis of BC in Arab women is substantially younger than Jewish women in Israel (by 8–10 years), with most Arab women (79%) being diagnosed premenopausally and 11% being diagnosed under the age of 35 years [6]. Early age at diagnosis is suggestive of an inherited predisposition to BC. Furthermore, given the Muslim Arab practice of endogamy, it seems plausible that recessively inherited genes may underlie inherited predisposition to BC in that population, as previously predicted [7]. Notably, no autosomal recessive genes have been reported thus far as contributors to inherited BC, but biallelic mutations in other cancer susceptibility genes (e.g., *MSH2 MSH6, MUTYH*) have been reported to be associated with cancer predisposition [8, 9]. Given the availability of massive parallel sequencing and the increase use of clinically validated "cancer panel testing" [10–13], the present study focused on non-Jewish individuals in Israel who were clinically assigned a high breast/ovarian cancer risk status based on clinically applied and acceptable criteria, who underwent next-generation sequencing of a 30-gene panel test for hereditary cancer risk (Color Genomics).

Materials and methods

Participant identification and recruitment The study population was recruited from among individuals counseled and tested at the Oncogenetics service located at the Sheba Medical Center, Tel-Hashomer, or the Ziv Medical center Safed, since January 1, 2000. Participants recruited were diagnosed with either breast, ovarian, or colon cancer from "high-risk breast/ovarian cancer families" based on well-accepted criteria [14; NCCN guidelines- https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#genetics_screening]. All study participants were unrelated to each other (i.e., only one patient per family was included). The study was approved by the local IRB and the ethics committee of the ministry of health, and each patient provided informed consent. Comprehensive data including demographics, reproductive history, exposures, and detailed family and personal history of cancer were obtained from each case. Cancer diagnoses were confirmed by pathological reports. Ethnicity was self-reported based on the ethnic origin and country of residence of all 4 grandparents.

DNA extraction Peripheral blood leukocyte DNA was extracted using the Puregene kit (Gentra Inc., Minneapolis, MN.) using the manufacturer's recommended protocol.

Color Genomics genetic test All samples underwent next-generation sequencing for a 30-gene panel for hereditary cancer risk provided by Color Genomics. The subsequent pipeline analyses and validation have previously been described [15].

Results

Participants' characteristics Overall, there were 68 participants in the study, each representing a unique high-risk breast/ovarian cancer family: 32 Druze, 26 Muslim-Palestinian Arabs, and 10 Christian Arabs. Fifty-nine were breast cancer cases [mean age at diagnosis (±SD) 42.7 ± 7.6 years, range 31–59 years), and 9 were ovarian cancer cases (mean age at diagnosis 51.6 ± 9.7 years, range 41–72 years), all with a significant family history of breast/ovarian/other cancer. There were 39 women who were diagnosed with breast cancer at or under 40 years of age. The mean age at genotyping was 45.3 ± 6.4 years. There were 91 first-degree relatives with breast cancer, 18 first-degree relatives with ovarian cancer, and 11 with other cancer types (gastric, pancreatic, CNS tumors).

Color genetic test results Overall in 3/68 high-risk breast/ovarian cancer cases, there were 3 heterozygous pathogenic or likely mutations in *BRCA1 PALB2* and *BRIP1*. Table 1 summarizes the results of the pathogenic and likely pathogenic mutations detected and the associated phenotype in these individuals and their families. In addition, 28 VUS were also detected (supplementary Table 1), and one additional VUS co-occurred in 1 individual with a pathogenic mutation (Table 1). Notably, in 36 cases no gene tested showed any sequence variant.

Discussion

In the present study, only a handful of families (3/68–4.4%) of non-Jewish, mostly of Druze origin, in Israel with features suggestive of inherited breast/ovarian cancer predisposition could be accounted for by mutations in any of the known major and moderate cancer susceptibility genes. Notably, of these genotyped individuals representing 68 unique families with inherited breast (and ovarian) cancer predisposition and/or women diagnosed with BC under age 45 years, only one woman carried a pathogenic *BRCA1* mutation (1.4%), another woman carried a

Table 1 Phenotype and genotype of the pathogenic and likely pathogenic mutation carriers in the study

Ethnicity	Clinical Dx	Cancer Dx age	Cancer in other family members	Gene	cHGVS	pHGVS	Classification
Christian Arab	HBC	BC 48	Sister BC 30, brother leukemia 68	PALB2	c.3350 + 4A > G	IVS12 + 4A > G	P
Druze	HBC	BC 35	Sister BC 40, sister BC 50,	BRIP1	c.1510dup	p.Ile504Asnfs*7	P
			mat aunt Gas 50, mat aunt endo ca 55	ATM	c.8734A > G	p.Arg2912Gly	VUS
Druze	LS like	OvC 49	Brother CRC 55	BRCA1	c.1039_1040delCT	p.Leu347Valfs*2	P

Dx diagnosis, *Gas* gastric cancer, *CRC* colorectal cancer, *BC* breast cancer, *HBC* hereditary breast cancer, *LS* Lynch syndrome, *mat* maternal, *pat* paternal, *OvC* ovarian cancer, *P* pathogenic, *VUS* variant of unknown significance

seemingly pathogenic *PALB2* mutation, and a third with a *BRIP1* mutation. While the role of *BRCA1* and *PALB2* as major BC susceptibility genes is well established, the role, if any, that *BRIP1* mutations play in BC susceptibility has recently been questioned [16].

Our previous study [17] that reported the results of comprehensive *BRCA1 and BRCA2* genotyping revealed that six of 45 Arab Moslem (Palestinian) women (13.3%) and 2 of 17 Druze individuals (11.7%) carried a pathogenic *BRCA1* or *BRCA2* mutation (Table 2). All but one of these previously reported *BRCA1* or *BRCA2* mutations were unique, and none was recorded in the present study. Specifically, there are only a handful of *BRCA1* and *BRCA2* gene germline mutations in the Palestinian population, in addition to the ones described by us previously [17]: an inactivating mutation (E1373X) in *BRCA1* [18] and another clearly pathogenic mutation (2482delGACT) in *BRCA2* [19]. Of note, a recent study from Israel reported a recurring, seemingly pathogenic missense mutation in the *TP53* gene [c.541C > T, R181C (rs587782596)] in 5/42 (11.9%) BC Palestinian Arab women who reside near Jerusalem, and speculated that this may be a "founder" mutation in this population [20]. None of the Muslim individuals genotyped herein was a carrier of any TP53 mutation, nor did we find the p. R181C**TP53* mutation when genotyping a set of 87 unrelated Muslim BC cases or in 245 cancer-free ethnically matched controls (Friedman E: unpublished data).

Such a low rate of *BRCA* mutations and, in fact, even when using panels of the major cancer susceptibility genes is also reported for other Middle Eastern populations. In a study from Saudi Arabia (and Canada), 10 Saudi women (and 10 Canadian women) with BC deemed at high risk for BC were genotyped using a 23-gene panel [BROCA- (http://web.labmed.washington.edu/tests/genetics/BROCA)]. Of the 59 sequence variants in the Saudi cases, most noted in the *BRCA1, BRCA2*, and *TP53* but seemingly deleterious mutations were also detected in the *MRE11 RAD51C BRIP1* confined to Saudi women only [21]. Even when more comprehensive genetic analyses were carried out in Middle Eastern populations, the results showed a limited number of cases accounted for by mutations in known major and moderate cancer susceptibility genes. In a study that performed whole exome sequencing on 45 Lebanese high-risk breast cancer cases, 19 mutations in 13 cancer susceptibility genes were reported, mostly *BRCA1* or *BRCA2* mutations, but mutations in *TP53, CHEK2, MSH2*, and *ATM* were also reported [22]. Merdad and coworkers [23] also performed a limited ($n = 7$) whole exome sequencing in Saudi Arabian BC cases and found *BRCA2* mutations but no mutations in any other "classical" BC susceptibility genes.

The data presented in this study, combined with these previous reports that focused on Muslim Arab populations

Table 2 Pathogenic mutations in *BRCA1* and *BRCA2* in Muslim and Druze individuals (adopted from Reference 17)

Ethnicity (# of families)	Exon	Base change	Effect on protein
BRCA1			
Druze	11	c.4160delAG	p.Gly1348AspfsX7
Druze	11	c.2277 G > T	p.E720X
Moslem	15	c.4643 G > A	p.W1508X
BRCA2			
Moslem (2 distinct families)	10	c.1991del4	p.Asn588SerfsX25
Moslem	11	c.6855del8	p.Ile2209MetfsX13
Moslem	23	c.9256ins4	p.His3010LeufsX22
Moslem	Intron 24	c.9485-1 G > C	Splice site mutation

in the Middle East, signify that despite theoretical predictions and assumptions that the spectrum of mutations in *BRCA1 BRCA2* among Palestinians is limited, the reality is that like most world populations a full analysis of both genes is warranted in the appropriate clinical setting. Notably, all but one of the mutations were detected only once. This lack of apparent "founder mutations" in both *BRCA1* and *BRCA2* genes in the Arab (Muslim, Christian) and Druze populations is intriguing. Despite the fact that the Druze sect is a clear example of a social and genetic isolate, there are no predominant or recurring mutations among high-risk families of Druze origin. Several reasons could account for the low rate of detection of mutations in *BRCA1* and *BRCA2* or other cancer susceptibility genes in these ethnic populations: low threshold of selection, inadequate selection criteria, phenocopies that were analyzed, or the reduced rate of *BRCA1/BRCA2* carriership predicted in societies where consanguineous marriages have been practiced. Notably, the risk for cancer in inbred populations was reportedly lower than in outbred populations [24] though not all studies concur [25].

This study has limitations that should be pointed out. First, the limited number of individuals tested and the targeted gene panel applied preclude any far-reaching conclusions. Second, the population selected was derived from individuals treated in two medical centers in Israel and do not reflect the entire diversity of the non-Jewish populations in Israel, with underrepresentation of the Palestinian population in the West bank and Gaza.

In conclusion, using a targeted gene panel a few pathogenic mutations in the known major and moderate breast/ovarian cancer susceptibility genes were detected, while most inherited cancer cases in the tested population remain unaccounted for. Future studies should expand the number of genes tested and preferably employ an unbiased sequencing scheme such as whole exome or whole genome sequencing.

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Compliance with ethical standards

Conflict of interest Alicia Y. Zhou and Jeroen van den Akker are employed by Color Genomics and are Color Genomics stockowners. All other authors declare no conflicts of interest.

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