Breast Cancer Research and Treatment (2019) 178:231–237
https://doi.org/10.1007/s10549-019-05379-6

EPIDEMIOLOGY

The yield of full *BRCA1/2* genotyping in Israeli Arab high-risk breast/ovarian cancer patients

Rinat Bernstein-Molho[1,15] · Inbal Barnes-Kedar[2] · Mark D. Ludman[3] · Gili Reznik[4] · Hagit Baris Feldman[4,5] · Nadra Nasser Samra[6,7] · Avital Eilat[8] · Tamar Peretz[9] · Lilach Peled Peretz[10] · Tamar Shapira[11] · Nurit Magal[2] · Marina Lifshitc Kalis[2] · Rinat Yerushalmi[12] · Chana Vinkler[13] · Sari Liberman[14] · Lina Basel-Salmon[2,16] · Mordechai Shohat[11] · Ephrat Levy-Lahad[14] · Eitan Friedman[15,16] · Lily Bazak[2] · Yael Goldberg[2,11]

Received: 22 May 2019 / Accepted: 25 July 2019 / Published online: 31 July 2019

Abstract

Purpose While the spectrum of germline mutations in *BRCA1/2* genes in the Israeli Jewish population has been extensively studied, there is a paucity of data pertaining to Israeli Arab high-risk cases.

Methods Consecutive Israeli Arab breast and/or ovarian cancer patients were recruited using an ethically approved protocol from January 2012 to February 2019. All ovarian cancer cases were referred for *BRCA* genotyping. Breast cancer patients were offered *BRCA* sequencing and deletion/duplication analysis after genetic counseling, if the calculated risk for carrying a *BRCA* mutation by risk prediction algorithms was ≥10%.

Results Overall, 188 patients participated; 150 breast cancer cases (median age at diagnosis: 40 years, range 22–67) and 38 had ovarian cancer (median age at diagnosis: 52.5 years, range 26–79). Of genotyped cases, 18 (10%) carried one of 12 pathogenic or likely-pathogenic variants, 12 in *BRCA1,* 6 in *BRCA2*. Only one was a rearrangement. Three variants recurred in more than one case; one was detected in five seemingly unrelated families. The detection rate for all breast cancer cases was 4%, 5% in bilateral breast cancer cases and 3% if breast cancer was diagnosed < 40 years. Of patients with ovarian cancer, 12/38 (32%) were carriers; the detection rate reached 75% (3/4) among patients diagnosed with both breast and ovarian cancer.

Conclusions The overall yield of comprehensive *BRCA1/2* testing in high-risk Israeli Arab individuals is low in breast cancer patients, and much higher in ovarian cancer patients. These results may guide optimal cancer susceptibility testing strategy in the Arab–Israeli population.

Keywords Israeli Arabs · Breast cancer · *BRCA1* · *BRCA2* · Recurrent mutations · Ovarian cancer

Introduction

The clinical significance and implications of identifying germline *BRCA1/2* mutations in cancer patients and in healthy individuals has been described extensively in the literature [1, 2]. While in most outbred populations there are family-specific, unique mutations, specific ethnic groups exhibit a more limited spectrum of recurrent mutations—the Icelandic, Polish and the Jewish Ashkenazi populations are notable examples [3].

The non-Jewish population comprises ~ 20% of the Israeli population, encompassing ~ 1.8 million individuals, the majority of whom are Muslim Arabs, with Christian Arabs and Druze forming the rest [4]. The Israeli Arabs are part of the Palestinian community that also resides in the West Bank, the Palestinian Authority and the Gaza Strip, and includes Palestinian refugees in Jordan, Syria and Lebanon [5]. This community, traditionally advocated and practiced consanguineous marriage, and has originated from Middle Eastern ancestors. These features made it plausible to assume that a limited spectrum of mutations in the *BRCA* will be defined in this population, akin to the situation in Israeli Jews.

Rinat Bernstein-Molho and Inbal Barnes-Kedar contributed equally to this work.

✉ Yael Goldberg
yaelgo43@gmail.com

Extended author information available on the last page of the article

Israeli National Cancer Registry (INCR—(https://www.health.gov.il/English/MinistryUnits/HealthDivision/Icdc/Icr/Pages/default.aspx) data indicate that breast cancer rates among non-Jewish (mostly Muslim Arab) women in Israel are lower than among Jewish women: breast cancer age-standardized incidence rate (ASR) are 56.1/100,000 in non-Jews, compared to 89.4/100,000 in Jewish women. However, in Mediterranean countries breast cancer is often diagnosed in premenopausal women [6, 7] and the median age at diagnosis is younger compared with Western European countries [8]. These differences in breast cancer phenotype are similar to those observed between African American and Caucasian populations. These phenotypic and clinical features differences may in part be attributed to differences in breast cancer risk factors, including genetic predisposition [7, 9, 10].

While there are studies that focused on Arab populations in Saudi Arabia, North African countries, Egypt and the Palestinian Authority, regarding the range of *BRCA* gene mutations in these countries [11, 12], there is a paucity of data regarding the yield of *BRCA* sequencing among high-risk Arab patients residing in Israel [13, 14].

The aim of this study was to evaluate the rate and spectrum of *BRCA1/2* mutations in Israeli Arab high-risk breast cancer and/or ovarian cancer patients.

Methods

Population study

Population study consisted of non-Jewish patients from the two main HMOs in Israel, affected with breast cancer and/or ovarian cancer, who had genetic counseling between January 2014–February 2019, and found eligible for comprehensive *BRCA* testing, For breast cancer cases all genotyped individuals had a 10% or more predicted risk for harboring a *BRCA* mutation based on, BRCAPRO, PENN II, or Myriad BRCA Risk Calculator prediction models [15–17]. *BRCA* sequencing and deletion/duplication analysis was performed in one of four large genomic laboratories (Recanati Genetics Institute Molecular Genetics Laboratory, Galil Genetic Analysis -GGA; Pronto Diagnostics, and Gene-by-Gene).

DNA isolation

Genomic DNA was extracted from peripheral blood using a MagNA Pure LC DNA Isolation Kit-LargeVolume and an automated Magna Pure LC2.0 instrument (Roche Diagnostics) according to manufacturer's instructions.

Genotyping methodology

BRCA1/2 sequencing, deletion/duplication analysis and assessment of pathogenicity of variants were performed as previously described [18].

Results

Study participants

The study cohort included 188 (185 females) unrelated patients, 146 of whom (78%) were Muslim, 30 (16%) Christians, 8 (4%) Bedouins and 4 (2%) Druze. Clinical characteristics of the study participants are presented in Table 1. Unilateral breast cancer was diagnosed in 128 (68%) women and 3 men, 19 (10%) women had bilateral breast cancer, 34 (18%) had ovarian cancer and 4 (2%) had both breast cancer and ovarian cancer. Age of diagnosis of breast cancer ranged from 22 to 67 years (median: 40 years), and age of ovarian cancer diagnosis ranged from 26 to 79 years (median: 52.5 years). Seventy-seven patients (41%) were diagnosed with cancer before the age of 40 years and 145/188 (77%) before 50 years of age. Family history of breast cancer or ovarian cancer among first or second-degree relatives was reported in 116 (62%) of patients. Nine patients (5%) reported family history of pancreatic cancer, and 16 (9%) reported prostate cancer in the family. All breast cancer cases had a probability of at least 10% of carrying deleterious *BRCA* variants as determined by at least one of the prediction models; of these, 104 had risks higher than 15%.

Genotyping results

Of 188 participants, 18 (9.6%) carried one of 12 pathogenic or likely pathogenic variants in *BRCA1/BRCA2* (Table 2). Pathogenic variants were detected in 11% of Muslim Arab patients and in 7% of Christian Arabs. Twelve (67%) patients carried *BRCA1* mutations and 6 (33%) *BRCA2* mutations. Only one gene rearrangement was detected. Variants of unknown significance (VOUSs) were reported in 20 (11%) patients.

Pathogenic or likely pathogenic variants were identified in 4% of patients with unilateral breast cancer, and in 5% of patients with bilateral breast cancer. None of the 3 men with breast cancer carried a *BRCA* pathogenic or likely pathogenic variant. The detection rate was 3% (2/71) for women who were diagnosed with breast cancer at age younger than 40 years, 5% (3/56) for women diagnosed between 40 and 49 years, 6% (1/17) for women between 50 and 60 years. None of the 8 patients diagnosed with breast cancer under

Table 1 Characteristics of patients referred to full sequencing of *BRCA1/2*

	Patients number (%)	Carriers		
		Number	% Out of all patients	% Out of carriers
All patients	188	18	9.6	100
Female/male	185/3	18/0	100/0	100/0
Age at first cancer diagnosis				
< 40	77 (41)	2	2.6	11
40–49	68 (36)	7	10.3	39
50–60	30 (16)	5	16.6	28
> 60	13 (7)	4	30.7	22
Age at BC first diagnosis				
< 40	71 (48)	2	3	33
40–49	56 (38)	3	5	50
50–60	17 (12)	1	6	17
> 60	3 (2)	0	0	0
Diagnosis				
Breast cancer	147 (78%)	6	4	
Unilateral breast cancer	128 (68)	5	4	28
Bilateral breast cancer	19 (10)	1	5	5
Ovarian cancer	38 (20)	12	32	
Ovarian cancer only	34 (18)	9	26	50
Breast and ovarian cancer	4 (2)	3	75	17
Male breast cancer	3 (2)	0	0	0
Ethnicity				
Muslim Arab	146 (78)	16	11	89
Christian Arab	30 (16)	2	7	11
Druse	4 (2)	0	0	0
Bedouin	8 (4)	0	0	0
Family history- OC and/or BC				
Yes	116 (62)	13	11	73
No	72 (38)	5	7	27
Family history-prostate cancer				
Yes	16 (9)	2	12	11
No	172 (91)	16	9	89
Family history-pancreatic cancer				
Yes	9 (5)	0	0	0
No	179 (95)	18	100	100

BC breast cancer, *OC* ovarian cancer

age 30 years were found to carry a *BRCA* mutation (Table 2). The youngest age of disease among carriers was 30 years (*BRCA1*) for breast cancer, and 43 years (*BRCA1*) for ovarian cancer.

Of patients with ovarian cancer (with and without breast cancer), 32% (12/38) carried pathogenic variants. Mutation detection rates were 26% for women diagnosed with ovarian cancer only, and reached 75% (3/4) in women with both breast cancer and ovarian cancer (Table 1).

The majority (13/18–73%) of carriers had positive family history of breast cancer/ovarian cancer, while only 2/18 (11%) had family history of prostate cancer, and none had reported pancreatic cancer in the family (Table 1). In 4 of the carriers, there was no discernable family history of cancer.

One likely pathogenic variant, c.5074+3A>G in *BRCA1*, was detected in 5 reportedly unrelated Muslim Arab patients from the same village, and two pathogenic variants occurred twice in apparently unrelated patients.

Table 2 *BRCA1* and *BRCA2* pathogenic and likely pathogenic variants in Arab patients

Gene	DNA change	Protein change	ACMG classification	No of patients	Ancestry	Diagnosis (age of diagnosis)	Family history
BRCA1	Exons 5-7 del		5	1	Muslim Arab	OC (47)	No
	c.1224delA	p.Val409*	5	1	Muslim Arab	OC (43)	BC + OC
	c.4523G>A	p.Trp1508*	5	1	Muslim Arab	OC (51)	BC
	c.5074+3A>G		5	5	Muslim Arab	OC (54)	BC + Prostate Ca
						BC (51) + OC (62)	BC + OC
						BC (52) + OC (46)	BC
						OC (57)	OC
						OC (64)	BC
	c.5161C>T	p.Gln1721Ter	5	1	Muslim Arab	Bilateral BC (30)	BC
	c.5309G>T	p.Gly1770Val	5	1	Muslim Arab	OC (73)	BC
	c.5444G>A	p.Trp1815*	5	2	Muslim Arab	BC (42) + OC (53)	BC
					Christian Arab	BC (39)	BC
BRCA2	c.3847_3848delGT	p.Val1283Lysfs*2	5	1	Muslim Arab	BC (46)	Prostate Ca
	c.4284dupT	p.Gln1429Serfs*9	5	2	Muslim Arab	OC (64)	No
						OC (73)	No
	c.6685G>T	p.Glu2229*	5	1	Muslim Arab	BC (40)	BC
	c.7024C>T	p.Gln2342*	5	1	Muslim Arab	BC (40)	No
	c.8332-3C>G		4	1	Christian Arab	OC (56)	BC
Total	12			18			

ACMG American College of Medical Genetics, *BC* breast cancer *OC* ovarian cancer

* Ter

Discussion

In this study, the yield of comprehensive *BRCA* testing in Israeli Arab high-risk breast cancer and/or ovarian cancer cases was ~ 10%, with lower rate of 4% for high-risk breast cancer patients. Twelve different pathogenic variants were identified in 18 cases, only one was a large rearrangement. This detection rate in breast cancer patients is lower than the reported rates in other Mid-Eastern populations [19–21]. Consistent with the findings in the current study, in a previous study, the rate of *BRCA* mutations in the non-Jewish population in Israel was also low—only 1/68 breast and ovarian patients carried a pathogenic variant [14]. Lolas Hamameh et al. have reported (in a cohort of Palestinian patients from the West Bank, Gaza strip and East Jerusalem) a 6.8% prevalence of mutations in *BRCA1/2* genes and an additional 6.7% of patients with mutations in other breast cancer susceptibility genes in a series of cases diagnosed with breast cancer by age 40 or with family history of breast cancer/ovarian cancer in a first or second degree relative [12]. In that study, a seemingly recurrent mutation, *BRCA2* c.2482delGACT, (0.7%, 6/875) was noted that was notably not detected in our cohort.

Several explanations may account for the lower than predicted detection rates in both BRCA genes in high-risk Arab population in Israel. First, germline-pathogenic variants in other breast cancer susceptibility genes. This notion seems to be supported by the fact that none of the patients who had breast cancer < 30 of age, and only 2/71 (3%) who were diagnosed with breast cancer under 40 years of age were *BRCA* gene carriers. In addition, family history of prostate and/or pancreatic cancer was not associated with *BRCA* mutations. Another plausible explanation for the discrepancy in observed vs expected mutation detection is that VOUs that were reported in 11% of genotyped individuals may, in fact, represent pathogenic variants in this population. Noteworthy, pathogenicity assignment was limited in some of the reported VOUSs as they novel or rare and insufficient functional data to accurately assign pathogenicity was available. The higher predicted mutation detection compared with the observed mutation detection rate could also be partially accounted for by the fact that these models were validated predominantly in Western, Caucasian population which is genetically different from the population in our cohort. The prevalence of *BRCA* mutations has never been assessed in the Israeli Arab population. If lower than used by the models, it could explain their inaccuracy. Lastly, the perceived

inherited predisposition in the current study participants (based on familial clustering and/or age at diagnosis) may in fact be due to a combination of environmental and multiple low-penetrance genetic factors. Indeed, previous studies focusing on Arab high-risk population in Israel [12, 14] support the notion that carriers of mutations in non-BRCA genes may have been detected in our cohort if multi-gene panel testing had been performed.

Comparison between three probability prediction models demonstrated significant *variability* in their clinical applicability, accuracy and performance [18, 22]. This reflects the inherent differences between the models, resulting in higher sensitivity of some and higher specificity of others [22].

As previously suggested [23], all patients with ovarian cancer should be offered comprehensive *BRCA1/2* genotyping, as defining *BRCA* carrier status has potential therapeutic implications (i.e., treatment with PARP-inhibitors) [24]. Indeed, the rate of mutation detection among ovarian cancer cases in the present study was 32%. Even if all five carriers of the same variant c.5074+3A > G in *BRCA1*, represent the same extended family, detection rates in ovarian cancer cases remains high—23% (7/31). These rates, that are in line with other studies in outbred populations, certainly justify *BRCA* genotyping for all ovarian cancer cases, regardless of family history.

The recurrent variant c.5074+3A > G in *BRCA1*, detected in 5 seemingly unrelated patients from the same village, probably represents a founder mutation. The same variant, also detected in two other Arab cohorts, from Israel [12] and Jordan [21], has been reported to affect splicing [25]. This variant does not have a gnomAD exomes entry, though its locus is covered in gnomAD exomes. It is categorized in ClinVar as a variant with conflicting interpretations of pathogenicity. Based on its effects on splicing and its occurrence in high-risk cancer affected women of Palestinian origin we suggest that this be re-assigned a likely pathogenic status.

Three mutations in *BRCA1* (c.1224delA, c.5074+3A > G, c.5444G > A,) and one mutation in *BRCA2* (c.6685G > T) detected in this study were previously reported by Lolas Hamameh et al. in another cohort of Palestinian patients from West Bank, Gaza and East Jerusalem [12]. The same *BRCA2* c.6685G > T and the *BRCA1* c.5074+3A > G mutations were also described previously in a Jordanian cohort of breast cancer patients [21]. In light of the historical background of Muslim population in this area, these common mutations probably reflect family ties or represent a common ancestor. However, none of the other detected mutations in our cohort were reported in other populations from the Middle East [26]. Some were either reported as founder or recurrent mutations in other populations, such as *BRCA1* c.5309G > T in Morocco [27], or in diverse populations worldwide according to the BIC database [28]. These findings may suggest ethnic and genetic associations between seemingly unrelated populations, or that some of these mutations involve mutational hotspots. Awareness of these recurrent mutations may be exploited for a useful strategy for focused genotyping platform in this population.

In conclusion, *BRCA1/2* mutations account for ~ 4% of the high-risk Arab, mostly Muslim, breast cancer patients in Israel, and for a much larger fraction of high-risk ovarian cancer cases. These findings suggest that all ovarian cancer cases should be offered comprehensive *BRCA* testing. Regarding breast cancer patients, as the majority of carriers had a family history of breast/ovarian cancer, positive family history should be scored and prompt genotyping more than age of diagnosis.

Several recurrent mutations in *BRCA1* [29], *CHEK2* [30], *TP53* [12, 31], *MSH2, MSH6* and *PMS2* [32–34] have been reported in the Arab population in the Middle East. It may be of benefit to implement a first pass genotyping platform that includes the recurring mutations for screening in this underserved population, followed by NGS multi-gene cancer panel for high-risk patients in whom none of these mutations was identified. Further studies are needed to gain knowledge and insight, and prioritize testing.

Funding This study was not funded by any grant.

Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Ethical approval All procedures performed in studies involving human participants 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. The study was approved by the IRB in the participating institutions.

Informed consent As data were aggregative and anonymous no informed consent was required by the institutional IRB.

References

1. Ford D, Easton DF, Stratton M, Narod S, Goldgar D, Devilee P et al (1998) Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. The breast cancer linkage consortium. Am J Hum Genet 62:676–689
2. Daly MB, Pilarski R, Berry M, Buys SS, Farmer M, Friedman S et al (2017) NCCN guidelines insights: genetic/familial high-risk assessment: breast and ovarian, version 2.2017. J Natl Compr Canc Netw 15:9–20
3. Karami F, Mehdipour P (2013) A comprehensive focus on global spectrum of BRCA1 and BRCA2 mutations in breast cancer. Biomed Res Int 2013:928562. https://doi.org/10.1155/2013/928562
4. The Central Bureau of Statistics. https://www.cbs.gov.il/en/subjects/Pages/Population.aspx. Accessed 16 Mar 2019
5. Spencer C. Tucker; Priscilla Roberts (12 May 2008). The Encyclopedia of the Arab-Israeli Conflict: A Political, Social, and Military

History [4 volumes]: A Political, Social, and Military History. ABC-CLIO. p. 503. ISBN 978-1-85109-842-2
6. Al-Kuraya K, Schraml P, Sheikh S, Amr S, Torhorst J, Tapia C et al (2005) Predominance of high-grade pathway in breast cancer development of Middle East women. Mod Pathol 18:891–897
7. Atoum MF, Al-Hourani HM (2004) Lifestyle related risk factors for breast cancer in Jordanian females. Saudi Med J 25:1245–1248
8. CI5 - Home [Internet]. Cancer Incid. Five Cont. Vol X Electron. Version. http://ci5.iarc.fr/Default.aspx. Accessed 15 Oct 2018
9. Bener A, Ayub H, Kakil R, Ibrahim W (2008) Patterns of cancer incidence among the population of qatar: a worldwide comparative study. Asian Pac J Cancer Prev 9:19–24
10. El Saghir NS, Khalil MK, Eid T, El Kinge AR, Charafeddine M, Geara F et al (2007) Trends in epidemiology and management of breast cancer in developing Arab countries: a literature and registry analysis. Int J Surg 5:225–233
11. Mahfoudh W, Bouaouina N, Ahmed SB, Gabbouj S, Shan J, Mathew R et al (2012) Hereditary breast cancer in Middle Eastern and North African (MENA) populations: identification of novel, recurrent and founder BRCA1 mutations in the Tunisian population. Mol Biol Rep 39:1037–1046
12. Lolas Hamameh S, Renbaum P, Kamal L, Dweik D, Salahat M, Jaraysa T et al (2017) Genomic analysis of inherited breast cancer among Palestinian women: genetic heterogeneity and a founder mutation in TP53. Int J Cancer 141:750–756
13. Laitman Y, Borsthein RT, Stoppa-Lyonnet D, Dagan E, Castera L, Goislard M et al (2011) Germline mutations in BRCA1 and BRCA2 genes in ethnically diverse high risk families in Israel. Breast Cancer Res Treat 127:489–495
14. Zidan J, Zhou AY, van den Akker J, Laitman Y, Schayek H, Schnaider J et al (2017) Inherited predisposition to breast and ovarian cancer in non-Jewish populations in Israel. Breast Cancer Res Treat 166:881–885
15. Parmigiani G, Berry D, Aguilar O (1998) Determining carrier probabilities for breast cancer-susceptibility genes BRCA1 and BRCA2. Am J Hum Genet 62:145–158
16. The Penn II Risk Model, BRCA 1 and BRCA 2 Mutation Predictor [Internet]. https://pennmodel2.pmacs.upenn.edu/penn2/index.jsp. Accessed 2 Sep 2017
17. BRCA Calculator [Internet]. http://www.myriadpro.com/brca-risk-calculator/calc.html. Accessed 7 Sep 2017.
18. Barnes-Kedar I, Bernstein-Molho R, Ginzach N, Hartmajer S, Shapira T, Magal N et al (2018) The yield of full BRCA1/2 genotyping in Israeli high-risk breast/ovarian cancer patients who do not carry the predominant mutations. Breast Cancer Res Treat 172:151–157
19. Jalkh N, Nassar-Slaba J, Chouery E, Salem N, Uhrchammer N, Golmard L et al (2012) Prevalance of BRCA1 and BRCA2 mutations in familial breast cancer patients in Lebanon. Hered Cancer Clin Pract 10:7
20. El Saghir NS, Zgheib NK, Assi HA, Khoury KE, Bidet Y, Jaber SM et al (2015) BRCA1 and BRCA2 mutations in ethnic Lebanese Arab women with high hereditary risk breast cancer. Oncologist 20:357–364
21. Abdel-Razeq H, Al-Omari A, Zahran F, Arun B (2018) Germline BRCA1/BRCA2 mutations among high risk breast cancer patients in Jordan. BMC Cancer 18:152
22. Cintolo-Gonzalez JA, Braun D, Blackford AL, Mazzola E, Acar A, Plichta JK et al (2017) Breast cancer risk models: a comprehensive overview of existing models, validation, and clinical applications. Breast Cancer Res Treat 164:263–284
23. Pal T, Permuth-Wey J, Betts JA, Krischer JP, Fiorica J, Arango H et al (2005) BRCA1 and BRCA2 mutations account for a large proportion of ovarian carcinoma cases. Cancer 104:2807–2816
24. Franzese E, Centonze S, Diana A, Carlino F, Guerrera LP, Napoli MD et al (2019) PARP inhibitors in ovarian cancer. Cancer Treat Rev 73:1–9
25. Menéndez M, Castellsagué J, Mirete M, Pros E, Feliubadaló L, Osorio A et al (2012) Assessing the RNA effect of 26 DNA variants in the BRCA1 and BRCA2 genes. Breast Cancer Res Treat 132:979–992
26. Farra C, Dagher C, Badra R, Hammoud MS, Alameddine R, Awwad J et al (2019) BRCA mutation screening and patterns among high-risk Lebanese subjects. Hered Cancer Clin Pract 17:4. https://doi.org/10.1186/s13053-019-0105-9
27. Quiles F, Teulé À, Martinussen Tandstad N, Feliubadaló L, Tornero E, del Valle J et al (2016) Identification of a founder BRCA1 mutation in the Moroccan population. Clin Genet 90:361–365
28. Online Research Resources Developed at NHGRI [Internet]. Online Res. Resour. Dev. NHGRI. https://research.nhgri.nih.gov/. Accessed 15 Oct 2018
29. Kadouri L, Bercovich D, Elimelech A, Lerer I, Sagi M, Glusman G et al (2007) A novel BRCA-1 mutation in Arab kindred from east Jerusalem with breast and ovarian cancer. BMC Cancer 7:14
30. Paperna T, Sharon-Shwartzman N, Kurolap A, Goldberg Y, Moustafa N, Carasso Y et al (2019) Homozygosity for CHEK2 p.Gly167Arg leads to a unique cancer syndrome with multiple complex chromosomal translocations in peripheral blood karyotype. J Med Genet. https://doi.org/10.1136/jmedgenet-2018-105824
31. Zick A, Kadouri L, Cohen S, Frohlinger M, Hamburger T, Zvi N et al (2017) Recurrent TP53 missense mutation in cancer patients of Arab descent. Fam Cancer 16:295–301
32. Goldberg Y, Barnes-Kedar I, Lerer I, Halpern N, Plesser M, Hubert A et al (2015) Genetic features of Lynch syndrome in the Israeli population. Clin Genet 87:549–553
33. Abu Freha N, Leibovici Weissman Y, Fich A, Barnes Kedar I, Halpern M, Sztarkier I et al (2018) Constitutional mismatch repair deficiency and Lynch syndrome among consecutive Arab Bedouins with colorectal cancer in Israel. Fam Cancer 17:79–86
34. Baris HN, Barnes-Kedar I, Toledano H, Halpern M, Hershkovitz D, Lossos A et al (2016) Constitutional mismatch repair deficiency in Israel: high proportion of founder mutations in MMR genes and consanguinity. Pediatr Blood Cancer 63:418–427. https://doi.org/10.1002/pbc.25818

Affiliations

Rinat Bernstein-Molho[1,15] · Inbal Barnes-Kedar[2] · Mark D. Ludman[3] · Gili Reznik[4] · Hagit Baris Feldman[4,5] · Nadra Nasser Samra[6,7] · Avital Eilat[8] · Tamar Peretz[9] · Lilach Peled Peretz[10] · Tamar Shapira[11] · Nurit Magal[2] · Marina Lifshitc Kalis[2] · Rinat Yerushalmi[12] · Chana Vinkler[13] · Sari Liberman[14] · Lina Basel-Salmon[2,16] · Mordechai Shohat[11] · Ephrat Levy-Lahad[14] · Eitan Friedman[15,16] · Lily Bazak[2] · Yael Goldberg[2,11]

1 Breast Cancer Center, Oncology Institute, Chaim Sheba Medical Center, Tel-Hashomer, Israel

2 Recanati Genetics Institute, Beilinson Hospital, Rabin Medical Center, Petach Tikva, Israel

3 Medical Genetics Institute, Meir Medical Center, Kfar Sava, Israel

4 The Genetics Institute, Rambam Health Care Campus, Haifa, Israel

5 The Ruth and Bruce Rappaport Faculty of Medicine, Technion – Israel Institute of Technology, Haifa, Israel

6 Genetic Unit, Ziv Medical Center, Tzfat, Israel

7 Faculty of Medicine, Bar Ilan University, Tzfat, Israel

8 Center for Clinical Genetics, Hebrew University Hadassah Medical Center, Jerusalem, Israel

9 Sharett Institute of Oncology, Hebrew University-Hadassah Medical Center, Jerusalem, Israel

10 The Genetics Institute, The Emek Medical Center, Afula, Israel

11 Maccabi Health Services, Rehovot, Israel

12 Davidoff Cancer Center, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel

13 Institute of Medical Genetics, Wolfson Medical Center, Holon, Israel

14 Medical Genetics Institute, Shaare Zedek Medical Center, Jerusalem, Israel

15 Susanne Levy Gertner Oncogenetics Unit,The Danek Gertner Institute of Human Genetics, Chaim Sheba Medical Center, Tel-Hashomer, Israel

16 The Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel