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Significantly lower rates of *BRCA1*/*BRCA2* founder mutations in Ashkenazi women with sporadic compared with familial early onset breast cancer

R. Gershoni-Baruch [a,b,*], E. Dagan [a,b], G. Fried [c], R. Bruchim Bar-Sade [d], R. Sverdlov-Shiri [d], G. Zelicksson [a], E. Friedman [d,e]

[a] *Department of Human Genetics, Rambam Medical Center, P.O.B. 9602, 31096 Haifa, Israel*
[b] *The Bruce Rappoport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel*
[c] *Department of Oncology, Rambam Medical Center, Haifa, Israel*
[d] *The Susanne-Levy Gertner Oncogenetics Unit, Institute of Genetics, Chaim Sheba Medical Center, Tel-Hashomer, 52621, Israel*
[e] *Department of Internal Medicine, Sackler School of Medicine, Tel-Aviv University, Tel-Aviv, Israel*

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Abstract

To delineate the clinical, genetic and family history attributes in Jewish Ashkenazi women with early onset (< 42 years) breast cancer we genotyped such women for the three predominant Jewish Ashkenazi mutations in *BRCA1* (185delAG and 5382insC) and *BRCA2* (6174delT). The study cohort was composed of 172 women diagnosed with breast cancer at or before the age of 42 years, obtained from the oncology department registry. Mutations were identified in 54 women (31%). Of 79 women with a positive family history for breast and/or ovarian cancer, and 93 with no such family history, 45 (57%) and 9 (10%), respectively, were mutation carriers ($\chi^2 = 46$; $P < 0.001$). Contralateral breast cancer occurred in 15 of 54 mutation carriers (28%) compared with 8 of 118 (7%) non-carriers ($\chi^2 = 14$; $P < 0.001$). Early onset breast cancer *per se* is a weak predictor of finding germ line mutation(s) in *BRCA1* and *BRCA2*, unless associated with a positive family history and/or bilaterality.

Keywords: *BRCA1*; *BRCA2*; Early-onset breast cancer; Hereditary breast cancer

1. Introduction

The majority of patients and families exhibiting inherited predisposition to breast cancer harbour germ line mutations in either *BRCA1* or *BRCA2* [1]. Uniquely, amongst Jewish Ashkenazi individuals, three founder mutations account for the overwhelming majority of mutations in high-risk families: 185delAG and 5382insC (*BRCA1*) and 6174delT (*BRCA2*). Moreover, these mutations are also detected in up to 2.5% of the general Ashkenazi population [2,3] whilst the 185delAG mutation was found in 0.5% of non-Ashkenazi Jews [4]. Features in patients with breast cancer considered indicative for and associated with an inherited genetic predisposition to developing the disease include: other affected family members (i.e. a positive family history of cancer), age at diagnosis under 42 years (early onset breast cancer), and syndromic association with second primary tumours (e.g. contralateral breast cancer, ovarian cancer) [5]. The notion of an early age of onset as a sole indicator of harbouring germ line mutation in breast cancer susceptibility genes has been directly addressed yielding inconclusive, conflicting results. Langston and colleagues [6] detected *BRCA1* germ line mutations in 6/80 (8%) of women with early onset breast cancer (< 35 years) who had a family history of breast and/or ovarian cancer, and in 2/39 (5%) of women who incurred breast cancer before the age of 35 years and reported no family history of cancer. In families with hereditary breast cancer, *BRCA1* germ line mutations were detected more frequently when breast cancer was diagnosed prior to the age of 40 years [7]. Moreover, in unselected Jewish Ashkenazi women with

* Corresponding author. Tel.: +972-4-854-2604; fax: +972-4-854-2441.

E-mail address: rgershoni@rambam.health.gov.il (R. Gershoni-Baruch).

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breast cancer diagnosed by age 40 years the rate of the specific founder mutations in *BRCA1* and *BRCA2* reached 26% [8,9]. Mutations were identified in 33% of Ashkenazi women diagnosed with breast cancer before age 42 years [10]. Overall, early age of onset seems to be strongly associated with an inherited genetic predisposition of developing breast cancer.

To appreciate the clinical and genetic attributes associated with early onset breast cancer, we genotyped 172 Ashkenazi women diagnosed with breast cancer at or before the age of 42 years for the three founder Jewish mutations in *BRCA1* and *BRCA2*.

2. Patients and methods

2.1. Patients

A retrospective study cohort was composed of 172 unrelated Jewish women (164 Ashkenazi and 8 non-Ashkenazi) diagnosed with breast cancer at/or before the age of 42 years. Our non-Ashkenazi patients were of Jewish Iraqi and Turkish descent, ethnic subgroups known to harbour the 185delAG mutation. These women were registered via the oncology department registries at Rambam and Sheba medical centres. The sole entry criterion for the study was early age at diagnosis. Eligibility included no restrictions on the time of diagnosis of breast cancer. None of these patients were registered because of a family history of breast or ovarian cancer.

The women were interviewed at our cancer genetic clinic between February 1996 and March 1999. Pathological confirmation of the diagnosis and a clinical and family history were available in every case along with blood samples. Family history was considered positive if one or more first- or second-degree relatives were affected with breast and/or ovarian cancer. Family history for cancers other than breast and/or ovarian was defined by one or more first- or second-degree relatives with any type of cancer other than breast and/or ovarian. All patients signed an informed consent form approved by the Institutional Review Board (IRB).

2.2. Genetic testing

Genomic DNA was extracted from peripheral blood samples by standard methods. Germ line mutations in *BRCA1* (185delAG, 5382insC) and in *BRCA2* (6174delT) were detected by polymerase chain reaction (PCR) and modified restriction analysis, as previously described [11,12]. PCR products were separated on 8% non-denaturating polyacrylamide gel, stained by ethidium bromide and visualised under an ultraviolet (UV) lamp.

2.3. Statistical analysis

The χ^2 or Fisher's Exact test was used for comparison between associations. Association between positive family history (first-degree and/or second degree, other family history and negative family history) and bilaterality, with carrier state was determined. Relative risks for being a carrier related to family history were calculated with their corresponding 95% confidence intervals. Logistic regression analysis was used to evaluate the contribution of family history (positive or negative for breast/ovarian or other type of cancer) and morbidity (unilateral or bilateral breast cancer) on the prediction of *BRCA* mutation.

3. Results

For the entire cohort ($n=172$) the mean age at diagnosis was 37±3.86 (range: 25–42). The study group was composed of: 79 (46%) women with a family history of breast and/or ovarian cancer (54 (31%) in a first-degree relative and 25 (15%) in a second-degree relative); 33 (19%) women with a family history of cancers other than breast and/or ovarian; and 60 (35%) women with no family history of breast and/or ovarian cancer (Table 1).

Overall, 54 mutation carriers (31%) were identified. Of these, 28 (16%) carried the 185delAG mutation, 14 (8%) had 5382insC mutation and 13 (8%) carried the 6174delT mutation (1 patient was a compound heterozygote for both the 185delAG and 6174delT mutations).

Table 1
Subdivision of patients with early onset breast cancer with regard to family history and carrier state

Family history of cancer	Carriers				Non-carriers	χ^2
	185delAG *n* (%)	5382insC *n* (%)	6174delT *n* (%)	Total *n* (%)	*n* (%)	
Breast/ovarian, first degree ($n=54$) second degree ($n=25$)	25[a] (32)	11 (14)	10[a] (13)	45 (57)	34 (43)	
Cancers other than breast/ovarian ($n=33$)	3 (9)	2 (6)	1 (3)	6 (18)	27 (82)	
Negative ($n=60$)	0	1 (2)	2 (3)	3 (5)	57 (95)	
Total ($n=172$)	28[a] (16)	14 (8)	13[a] (8)	54 (31)	118 (69)	$\chi^2=46$; $P<0.001$

[a] One patient was a double mutation carrier: heterozygote for mutations 185delAG and 6174delT.

Of 54 mutation carriers, 45 (83%) reported a history of breast and/or ovarian cancer in first- or second-degree relative/s, 6 (11%) had a positive family history for cancers other than breast and/or ovarian (in either first- or second-degree relative/s) and 3 patients (6%) not considered to have a positive family history still recorded a history of cancer in third-degree relative/s.

Mutations were identified in 45/79 (57%) patients with a family history of breast and/or ovarian cancer, in 6/33 (18%) patients with a family history of other cancers and in 3/60 (5%) patients with no family history of breast/ovarian or other type of cancer ($\chi^2 = 46$; $P < 0.001$) (Table 1).

The effect of positive family history in a first-degree relative, compared with a positive family history in a second-degree relative, on carrier state, was highly significant ($\chi^2 = 25$; $P < 0.001$). The carrier rate was higher amongst patients who had first-degree affected relative/s than amongst those who had only second-degree affected relative/s, a relative with cancer other than breast and ovarian or no affected relative. The estimates for being a carrier are higher in women with first- and in women with first- and second-degree relatives, affected with breast and/or ovarian cancer, compared with those with no such family history (RR = 7.85; 95% confidence interval (CI) 4.14–14.86 and RR = 5.86; 95% CI 3.07–11.27, respectively).

Contralateral breast cancer occurred in 15 of 54 mutation carriers (28%) and 8 of 118 non-carrier patients (7%) ($\chi^2 = 14$; $P < 0.001$). Amongst those with mutations, 5 had synchronous breast cancer, and 10 were diagnosed with a second breast cancer at a median of 7.8±5.8 years after initial diagnosis. All 8 non-carrier patients had metachronous contralateral breast cancer within a median of 8.5±8 years after initial diagnosis. The mean follow-up period in women with/without mutations did not differ (6.32±7.24 and 8.32±8.57 years, respectively).

In a model of logistic regression, the family history (positive or negative for breast/ovarian or other type of cancer) together with morbidity (unilateral or bilateral breast cancer) predict 75% of the carrier state.

4. Discussion

A family history of breast cancer is a well known risk factor for developing breast cancer, whereas inherited susceptibility to breast cancer is frequently manifested by early age of onset [5]. A high carrier frequency for *BRCA1* mutations ranging from 19% to 26% in Jewish women diagnosed before age 42 years was observed [8–10,13–15]. However, no clear delineation in the differential contribution of family history versus age of onset was reported. In this series, the frequency of a *BRCA1* or *BRCA2* mutation in women with early onset breast cancer was high (54/172; 31%), mainly attributed to mutations in *BRCA1*. Interestingly, 5382insC accounts for 26% (14/54) of mutations detected, an extremely high rate allowing for the low prevalence of this mutation in the general Ashkenazi population (0.2%) [3]. A strong association of *BRCA* mutations with positive family history for breast and/or ovarian cancer was noted. Amongst patients with early onset breast cancer with no family history of cancer, the frequency of mutation carriers (3/60; 5%) is double that detected in the general Ashkenazi population, whereas 57% (45/79) of women with early onset breast cancer and a positive family history for breast/ovarian cancer were mutation carriers. These results indicate that in Jewish Ashkenazi women with early onset disease, the likelihood of detecting one of the founder *BRCA1* or *BRCA2* mutations is primarily determined by eliciting a positive family history of cancer, rather than by the early age of onset *per se*. In women with early onset breast cancer, having a first-degree affected relative is a most important predictive determinant for being a mutation carrier. Additionally, our data show that the risk of a woman with early onset breast cancer to develop a contralateral breast cancer is 4-fold higher in mutation carriers than in non-carriers. Bilateral breast cancer associated with positive family history is highly predictive of being a mutation carrier. The results of this study should be taken into consideration during clinical decision making when assessing patients with early onset breast cancer. Specifically, patients with early age of onset who are mutation carriers should be counselled as to their high risk of developing contralateral breast cancer.

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