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Similar prevalence of founder *BRCA1* and *BRCA2* mutations among Ashkenazi and Non-Ashkenazi men with breast cancer: Evidence from 261 cases in Israel, 1976-1999

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Abstract

To evaluate the potential contribution of mutations in the BRCA1 and BRCA2 genes to male breast cancer (MBC), we expanded a previous study to screen a total of 261 Israeli men diagnosed with breast carcinoma. A total of 21 BRCA2 6174delT and eight BRCA1 185delAG mutations were found. Similar frequencies of BRCA1 and BRCA2 mutation carriers were found among Ashkenazi (12.8%) and non-Ashkenazi Jews (9.1%). The combined prevalence of BRCA1/BRCA2 founder mutations among Ashkenazi Jewish men is slightly higher than for women, due to a higher frequency of BRCA2 mutations.

1. Introduction

With approximately 1,700 new cases expected to occur in 2006, male breast cancer (MBC) accounts for only 0.7% of all breast cancer diagnosed in the US.(1) However, the disease incidence in the US is increasing and has climbed 26% over the past 25 years.(2) Similarly, the annual age-standardized incidence rate in Israeli Ashkenazi Jews (persons whose families immigrated to Israel from Europe or America) has been steadily increasing from 9 in 1980 to 12 per million in 1997.(3) In contrast, the annual rates among non-Ashkenazi Jews (people from families originating from Mediterranean regions), who comprise approximately 45% of the one million Jewish men over 40 years of age living in Israel,(4) remained around 7 per million over the same time period. Breast carcinoma has also been observed to be more common among American Jewish men, a population of predominantly Ashkenazi origin, compared to other non-Jewish Americans. (5-8)

The functionally defective mutations of BRCA1 and BRCA2 are associated with increased breast cancer risk; however, such mutations are relatively rare in unselected cancer patients. The frequency of three founder germline mutations in the tumor suppressor genes *BRCA1* and *BRCA2* among unselected Ashkenazi women with breast cancer is roughly 10%, and is much

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higher in multiple-case families.(9-11) These observations led us to conduct an earlier population-based study on these founder mutations of MBC patients in Israel. We found that 15% of the 89 Ashkenazi patients examined were carriers of the *BRCA2* 6174delT mutation. (12) Surprisingly, we also found two carriers of this mutation among 21 non-Ashkenazi MBC Jewish patients. This was the first published observation of this mutation among non-Ashkenazi Jews suggesting a common ancestor *BRCA2* 6174delT emerged prior to the divergence of these groups, similar to *BRCA1 185delAG* mutation.(13) Since our publication, two other studies of Ashkenazi men (14,15) have been published, but they had a relatively small number of cases (n<30). We therefore expanded our study by including patients from additional hospitals to better estimate the frequency of *BRCA1* and *BRCA2* mutations among Israeli MBC patients.

2. Patients and Methods

The current study includes all 269 MBC cases who were diagnosed in 16 hospitals throughout Israel between 1976 and 1999, including the 110 subjects in our first report.(12) The cases available for the study represent half of the total number of incident MBCs in the country during this period.(16) Eight subjects did not have adequate pathological material for mutation status and marker genotypes, leaving 261 in the study sample. The laboratory methods for the three founder mutations 185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2* were as previously described.(12)

Jewish patients were characterized either as Ashkenazi or non-Ashkenazi, based on the recorded place of birth in the Israeli Population Registry or, if they were born in Israel, their fathers' recorded place of birth. Patients who were born in the former USSR (n=52), other Eastern European countries (n=79), Central or Western Europe, (n=29), America (n=4), South Africa (n=1), or were born to fathers from these areas (n=23) were categorized as Ashkenazi Jews. Non-Ashkenazi Jews were either born in North Africa (n=27), the Middle East (n=15), Bulgaria (n=3), Greece (n=2), Ethiopia (n=2), Afghanistan (n=2), or their fathers were from those areas (n=4). Non-Jewish Israeli-born were designated as Arabs (n=16). Two patients born in Israel, who were sons of Israeli-born fathers, were categorized as undefined origin. We used the Fisher's exact test corrected for continuity to determine whether there was statistically significant difference in the frequency of mutation carriers between the study groups and the Mann Whitney test to compare their median age at diagnosis of the breast cancer.

The pathology material was de-identified prior to pathology review and statistical analysis. Due to the anonymous nature of the study design, medical records were not abstracted, and no information concerning stage at the time of diagnosis was obtained. The study was done under a waiver of the requirement for Institutional Review Board review granted by the National Institutes of Health Office of Human Subjects Research

3. Results

Excluding the two patients of undefined origin, Ashkenazi, non-Ashkenazi Jews, and Arabs comprised 63.2%, 19.5% and 6.1% of the study sample, respectively (table 1). This distribution is very similar to that reported for male breast cancer (62.1%, 19.6%, and 4.0%) in the Israel National Cancer Registry.(3,16)

Among the 151 new MBC cases, we detected 10 additional mutations (six 6174delT and four 185delAG), bringing the total number of *BRCA1* and *BRCA2* mutations in the combined study to 29 (table 2). All mutations were found among Jewish patients, representing a carrier frequency of 11.8%, whereas no mutation was found among the 16 Arab patients (P=0.12).

BRCA1 and *BRCA2* mutation carrier frequencies were not statistically different between Ashkenazi (12.8%) and non-Ashkenazi Jews (9.1%). It is of note that among 38 patients born in Romania, eight (21.1%) were mutation carriers (4 *BRCA1* and 4 *BRCA2*). The median age at diagnosis of the breast cancer among *BRCA1* mutation carriers was 63 years (range, 36-78) compared to 68 years (range, 32-90) and 72 (range, 32-82) among *BRCA2* mutation carriers and all non-carriers, respectively. However, these differences did not reach statistical significance (Mann Whitney test P>0.3).

4. Discussion

Our previous report (12) was the first to show two non-Ashkenazi patients with a *BRCA2* 6174delT mutation among the 21 non-Ashkenazi Jewish cases. The expanded data in the present study allowed the detection of two more cases of *BRCA2* and one case of *BRCA1* mutations, bringing the total prevalence of *BRCA1* and *BRCA2* mutations among the non-Ashkenazi Jewish patients to 9.1%, similar to that observed among the Ashkenazi Jewish patients.

The 3.3% frequency of *BRCA1* mutation prevalence among the Jewish patients in our study is comparable to the one in ten Ashkenazi patients from Israel found in a previous study (15) and to the one observed among 25 MBC cases in Italy.(18) Similar to other studies(19-22) we found no *BRCA1* mutation carriers among our 16 non-Jewish patients.

The 8.6% frequency of germline founder *BRCA2* mutation among the Jewish patients in the present study is lower compared to other examined samples,(18-20,22-26) although the prevalence has varied considerably, reaching as high as 40% in a population-based study of 30 MBCs from Iceland (24) and as low as 4% (95% CI: 5%-10%) (19) among 54 cases in Southern California (table 3). The relatively high variability in various populations may reflect genetic diversity, sample selection, or differences in type of mutation.

In female *BRCA1/2* mutation carriers, it is estimated that the risk for early-onset breast carcinoma is increased up to 20-fold compared to non-carriers, and before age 50 years, the average risk of breast cancer is significantly higher in *BRCA1* than in *BRCA2* mutation carriers. (27) The age of diagnosis among our male *BRCA1* mutation carriers was younger compared to BRCA2 carriers and non-carriers, however, this could be due to chance alone because of the small number of cases.

Our characterization of Jewish men as Ashkenazi or non-Ashkenazi was based on the place of birth as recorded in the Israeli Population Registry and not by biological testing or questionnaire. Therefore, some misclassification could occur, especially among the patients born in the Asian regions of the former USSR, who were categorized as Ashkenazi for the current study but who frequently (approximately 20% (28)) are non-Ashkenazi. However, the frequency of BRCA1 and *BRCA2* mutations among cases from the former Soviet Union was similar to the rest of the Ashkenazi Jewish population, suggesting that the misclassification is not likely to have a major effect on our results.

The *BRCA1* mutation involving insertion of a cytosine in *BRCA1* (5382insC) probably originated from the Baltic region.(29) It is the most common *BRCA1* mutation worldwide, and is particularly important in Russia (30) and Poland.(31) However, our results and a previous study of 1576 Jewish males (10) suggest that among Ashkenazi men, the prevalence of this mutation carriers is less frequent (<0.5%) than the *BRCA1* 185delAG mutation.

Comparison of the results of our original study (12) and the current data show a similar mutation frequency among Non-Ashkenazi Jews. Among Ashkenazi Jews, however, the prevalence of 6174delT mutation in our original study (13.6%) was significantly (P<0.01) higher compared

to 3.8% among later cases (n=105). Laboratory methods were the same in the two groups of subjects, and all earlier mutation carriers were verified. This difference may be explained in part by an increasing percentage of new immigrants who have only one Jewish parent, and Israeli born Jews who are of mixed Ashkenazi and non-Ashkenazi background (32). According to the recent Israel Central Bureau of Statistics,(4) 23% of the men above 30 years who immigrated to Israel after 1990 from the former USSR were born to non-Jewish mothers, and probably similar number were born to non-Jewish fathers. Since the newly analyzed cases were almost 5-fold more likely to be recent immigrants, this may have contributed to the difference in prevalence, which otherwise is likely to be due to chance.

In summary, in this study of the largest number of MBC cases published to date, we observed a frequency of founder *BRCA1/BRCA2* mutation carriers among Ashkenazi Jewish men with breast carcinoma that was lower than several earlier reports, including our own.(12) The prevalence was higher, but not dramatically so, than that observed in Ashkenazi women with breast cancer, due largely to a higher prevalence of the *BRCA2* mutation in men. Additionally, we observed a similar prevalence of the 6174delT mutation in *BRCA2* among non-Ashkenazi Jews. The study results suggest that the higher overall incidence of male breast cancer in Ashkenazi men compared to non-Ashkenazi men in Israel,(3) can not be explained only by differences in the prevalence of founder mutations 185delAG *BRCA1* or 6174delT *BRCA2*.

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Table 1

Distribution of study sample according to origin

	Jewish Immigrants and Arabs		Israeli-born Jews[a]		Total	
	n	(%)	n	%	n	%
Ashkenazi Jewish	165	(63.2%)	23	(8.8%)	188	(72.0%)
Non-Ashkenazi Jewish	51	(19.5%)	4	(1.5%)	55	(21.1%)
Arabs	16	(6.1%)	0	-	16	(6.1%)
Undefined	0	-	2	(0.8%)	2	(0.8%)
Total	232	(88.9%)	29	(11.1%)	261	(100.0%)

[a] According to father's place of birth

Table 2

Israeli male-breast-cancer (MBC) mutation testing results

		n tested	BRCA2 6174delT (%; 95%CI)	BRCA1 185delAG (%; 95%CI)	Total BRCA1/2 (%; 95%CI)
Jews		245	21 (8.6%; 5.4%-12.8%)	8 (3.3%; 1.4%-6.3%)	29 (11.8%; 8.1%-16.6%)
	Ashkenazi	188	17 (9.0%; 5.4%-14.1%)	7 (3.7%; 1.5%-7.5%)	24 (12.8%; 8.4%-18.4%)
	Non-Ashkenazi	55	4 (7.3%; 2.0%-17.6%)	1 (1.8%; ≤9.7%	5 (9.1%; 3.0%-20.0%)
	Undefined	2	0 (0%; ≤84.2%)	0 (0%; ≤84.2%)	0 (0%; ≤84.2%)
Arabs		16	0 (0%; ≤20.6%)	0 (0%; ≤20.6%)	0 (0%; ≤20.6%)
Total		261	21 (8.0%; 5.0%-12.0%)	8 (3.1%; 1.3%-5.9%)	29 (11.1%; 7.7%-15.4%)

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Table 3

Prevalence and 95%confidence interval (CI) of *BRCA1/2* mutations in epidemiological studies of male breast cancer (MBC)

Study	Population	n tested	*BRCA1* Carriers (%; 95%CI)*	Mutations	*BRCA2* Carriers (%; 95%CI)	Mutations
Jewish MBC						
Current[a]	*a. Ashkenazi Jews*	188	7 (4%; 2-7%)	185delAG	17 (9%; 5-13%)	6174delT
	b. Non-Ashkenazi Jews	55	1 (2%; 1-7%)		4 (8%; 2-17%)	
Frank et al (2002) (14)	MBC patients, USA.	55	8 (28%; 5-18%)		14 (18%; 11-28%)	
	a. Non-Ashkenazi Jews, USA.	48	10 (28%; 11-33%)[b]			
	b. Ashkenazi Jews, USA	28	11 (39%; 22-58%)[b]			
Sverdlov et al (2000) (15)	*a. High risk Ashkenazi Jews, Israel*	10	1 (10%; 0-34%)	185delAG	1 (10%; 0-34%)	6174delT
	b. Unselected Patients, Israel	21	0 (0%; 0-16%)		0 (0%; 0-16%)	
Any MBC						
Couch et al (1996) (25)	MBC patients, USA	50			7 (14%; 6%-26%)	Three 6174delT, 1128insG, 3038delAA, 6299delA, 7989delC
Friedman et al (1997)(19)	MBC patients, S. California	54	0 (0%; 0-7%)		2 (4%; 5-10%)	
Thorlacius et al (1997)(24)	MBC patients, Iceland	30			12 (40%; 23%-56 %)	999del5
Haraldsson et al (1998)(23)	MBC patients, Sweden	34			7 (21%; 9-36%)	G4186T, Three 4486delG, 6503delTT, 9326 insA, 9636delT
Csokay et al (1999) (20)	MBC/gynecomastia patients, Hungary	18	0 (0%; 0-19%)		6 (33%; 13-56%)	4232insA, 277delAC, 3868insT, 7979delG, 841insCTTA, 9326insA
Tirkkonen et al (1999)(21)	Invasive MBC patients, Sweden	26	0 (0%; 0-13%)		5 (19%; 7-36%)	G4186T, Two 4486delG, 6503delTT, 9326insA
Kwiatkowska et al (2001)(26)	MBC patients, Poland	37			4 (11%; 4-23%)	8138del5, 6495del3insC, 8457insA, 2034insA
Basham et al (2002) (22)	MBC patients, UK	94	0 (0%; 0-4%)		5 (5%; 2-11%)	253delC, 2192delC, 5974delCT, 7928delCT, 8474delAG
Ottini et al (2003) (18)	Population-based series of MBC, Italy	25	1 (4%; 0-14%)	3345delAG	3 (12%; 3-27%)	6696delTC, 1003delA, 6010G→T

[a] Data Include 4 and 12 cases of 185delAG and 6174delT mutations respectively, among 89 Ashkenazi cases and 2 cases of 6174delT mutation among 21 Non-Ashkenazi Jews cases which were described in our earlier report(12).

[b] Any Ashkenazi *BRCA1* or *BRCA2* founder mutations