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Double heterozygosity in the BRCA1 and BRCA2 genes in the Jewish population

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Background: The frequency and characteristics of disease in individuals who concomitantly harbor pathogenic mutations in both BRCA1 and BRCA2 genes are not established.

Materials and methods: Data were collected from the database of Clalit Health Services National Familial Cancer Consultation Service. Probands referred to this clinical service and their family members are routinely tested for the three Jewish founder mutations (BRCA1:185delAG, 5382insC, BRCA2:6174delT). In addition, carriers identified in a population-based cohort of all cases diagnosed with breast cancer in Israel in 1987–1988 allowed the estimation of the population frequency of this phenomenon.

Results: In the clinic-based series of 1191 carriers of mutations in BRCA1 or BRCA2 belonging to 567 families, 22 males and females (1.85%) from 17 different families (3.0%) were found to harbor two different mutations. These included 18 individuals (1.51%) who concomitantly carried the 185delAG BRCA1 and the 6174delT BRCA2 mutations and four individuals (0.34%) who carried the 5382insC BRCA1 and the 6174delT mutations. All individuals were heterozygote carriers and none had a double mutation of both founder mutations in the BRCA1 gene itself. Seven of the 16 double carrier women (46.7%) had a personal history of breast carcinoma, diagnosed at a mean age of 44.6, compared with 372/926 (40.2%) carriers of a single mutation diagnosed with a mean age at diagnosis of 48.1 [odds ratio (OR) = 1.3, 95% confidence interval (CI) 0.4–4.0]. One case (6.7%) had a personal history of ovarian carcinoma diagnosed at the age of 53 compared with 55/926 (5.9%) of the women with single mutation (OR = 1.1, CI = 0.2–7.6). The frequency of double mutations in the population-based national breast cancer cohort was 2.2% of all carriers, and 0.3% of all breast cancer cases in the Ashkenazi population in the cohort. The mean age at diagnosis of breast cancer was younger in the carriers of two mutations.

Conclusion: Double carriers of mutations in the BRCA genes are rare and seem to be carrying a similar probability of developing breast and ovarian cancers as carriers of single mutations.

Key words: Ashkenazi Jewish women, BRCA, double mutations

introduction

About 3% of Ashkenazi Jewish women carry one of three founder mutations in the BRCA1 (185delAG, 5382insC) and the BRCA2 (6174 delT) genes [1]. These mutations are associated with a dramatically increased lifetime risk of breast and ovarian carcinoma with an early manifestation [2, 3]. Approximately 10% of breast cancers and >30% of ovarian cancers in Ashkenazi Jewish women are the result of genetic predisposition due to germline mutations in the BRCA1 and BRCA2 genes [1, 3] While sporadic case reports of women with double mutations in both BRCA1 and BRCA2 are available [4–7], none came from systematic carriers series or from population-based studies. This study describes the frequency and characteristics of people heterozygote to more than one founder mutation in BRCA1 and BRCA2.

materials and methods

Data were evaluated from two sources: the Clalit Health Services National Familial Cancer Consultation Service in Israel and a historical national cohort of all women diagnosed with breast cancer in Israel in 1987–1988. The Familial Cancer Consultation Service evaluates physician-referred and self-referred probands or families with multiple cases of cancer [2]. The Service also consults all carriers detected through routine BRCA genetic testing of all participants in large population-based studies of cancer etiology conducted at the National Cancer Control Center. The 1987–1988 National cohort includes all women diagnosed with breast cancer in Israel in these years for whom a tissue block was available in 2002 for genetic analysis. The methods of this study have previously been described [1]. In

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brief, all individuals were tested for the three common BRCA mutations in the Ashkenazi Jewish population (185delAG and 5382insC on BRCA1 and 6174delT on BRCA2). In all study participants, only these three founder mutations have been tested for. The medical records of all participants were reviewed to the extent they were available. Data on types of cancer detected in carriers and age at diagnosis were sought. Proportion of multiple carriers was calculated among the clinical service families and in the breast cancer cohort. The proportion developing cancer and age at diagnosis were compared between double and single carriers using chi-square statistics with significant P values set at $P < 0.05$.

All data were collected from the various sources under approval of the Institutional Review Board committee of Carmel Medical Center in Haifa.

results

clinical series

During the years 1998–2008, 1191 of all people tested at the Familial Cancer Service, belonging to 567 different families, were found to be carriers of one of the three Jewish Ashkenazi BRCA genes mutations. Among them, 22 people (1.85% of carriers) from 17 different families (3.0% of families) were found to be carriers of double mutations. A total of 1.51% of the carriers carried both the 185delAG mutation in BRCA1 and the 6174delT mutation in BRCA2, and 0.34% carried the 5382insC mutation in BRCA1 and the 6174delT mutation in BRCA2. None of the carriers was a double carrier of the two Ashkenazi mutations in the BRCA1 gene (Table 1).

Of 22 double mutation carriers, 15 were females. Of them, seven (46.7%) have a history of breast cancer and one (6.7%) has a history of ovarian cancer. This is to be compared with 372 of 926 single mutation carrier women with history of breast cancer (40.2%) and 55 of 926 single mutation carriers with ovarian cancer (5.9%), representing no significant difference in the rate of breast cancer [odds ratio (OR) = 1.3, 95% confidence interval (CI) 0.4–4.0] or ovarian cancer in double carriers (OR = 1.1, 95% CI 0.2–7.6).

Double mutation carriers expressed their cancer at an earlier age (44.6 ± 13.5) than did single mutation carriers (48.1 ± 13.0). This was especially true for carriers with the double mutations 5382insC and 6174delT who were diagnosed at age 37.5 ± 13.5.

Prophylactic oophorectomy was carried out by three unaffected women, while prophylactic mastectomy was carried out by two. While the carrier who developed ovarian cancer died of her disease after 7 years from diagnosis, all of the seven women with breast cancer are still alive, after a mean follow-up period of 12.6 years.

Among 7 male carriers no cancers of the breast or prostate were detected. Two of the males were diagnosed with colorectal cancer, but they were both probands who were diagnosed

Table 1. Proportion of single and double carriers of Jewish founder mutations, risk of cancer and age at cancer diagnosis in the Israeli Familial Cancer Service series and Breast Cancer Cohort

	Number tested in carrier families	Number of all carriers (%)	Number of female carriers (%)	Affected females	Mean age of diagnosis of breast cancer
Clinical series	1779	1191	942		
Single mutation		1169	926		48.1 (±13.0)
BRCA1 185delAG		556 (46.68)	444 (47.13)	178 Breast (40.1%) 88 Ovary (19.8%)	46.8 (±12.3)
BRCA1 5382insC		181 (15.20)	151 (16.03)	72 Breast (47.7%) 20 Ovary (13.2%)	46.8 (±14.0)
BRCA2 6174delT		432 (36.27)	331 (35.14)	122 Breast (36.9%) 22 Ovary (6.6%)	50.8 (±13.0)
Double mutation		22 (1.85)	16 (1.70)	8 Breast 1 Ovary	44.6 (±13.5)
BRCA1 185delAG + BRCA2 6174delT		18 (1.51)	14 (1.49)	6 Breast (42.9%) 1 Ovary (7.1%)	47.0 (±13.5)
BRCA1 5382insC + BRCA2 6174delT		4 (0.34)	2 (0.21)	2 Breast	37.5 (±13.5)
BRCA1 185delAG + BRCA1 5382insC		0	0		
Breast cancer cohort study	1794 All 1102 AJ[a]	135	135	135	
Non-carriers		1659	1659	1659	62.1 (±13.5)
Single mutation					
BRCA1 185delAG		61	61	61	56.0 (±15.5)
BRCA1 5382insC		17	17	17	51.5 (±13.6)
BRCA2 6174delT		53	53	53	57.3 (±12.8)
Double mutation					
BRCA1 185delAG + BRCA2 6174delT		4 (0.30)	4 (0.30)	4	49.3 (±17.0)

[a]AJ, Ashkenazi Jews.

through a colorectal cancer case-control study conducted in our Center.

population-based breast cancer cohort

Of all 1794 breast cancer cases in the Israeli 1987–1988 breast cancer cohort, 1102 were Ashkenazi Jews. Of them, 135 (12.3%) were mutation carriers and 4 (0.3%) were carriers of both, mutations in BRCA1 and in BRCA2. Women carrying two mutations developed their breast cancer at an earlier age (49.3 $\pm$ 17.0) than those with single mutation; 56.0 $\pm$ 15.5 in BRCA1 carriers and 57.3 $\pm$ 12.8 in BRCA2 carriers.

Discussion

It is estimated that the likelihood of carrying a founder mutation in the BRCA1 and BRCA2 genes in the Ashkenazi Jewish population is ~3% [8, 9] reflecting about a 0.1% likelihood of carrying two different mutations. While ample data are available on the clinical behavior of single mutation carriers, the clinical data on carriers of two mutations are minimal and usually reflect single case reports [4–6, 10–13].

Previously described double heterozygote carriers of mutations in the BRCA genes have demonstrated a wide variability in age at onset and in probability of expression of breast and ovarian cancers. A clinic-based estimated prevalence of 1.8% was reported in a summary of available case reports [5]. This group had a mean age at breast cancer diagnosis of 40.8 and an 84% probability for breast cancer by age 70. The mean age for ovarian cancer was 45.7.

In the analysis of our single-institute, large population-geared service, a similar prevalence estimate of 1.85% was found, but the most valid estimate from the population-based study came up with a higher prevalence estimate of 2.2%. Similarly, a slightly younger age at diagnosis was noted in both, our clinic series and our population-based study. On the other hand, we did not notice an increased probability of expression of breast or ovarian cancer compared with single carriers.

We could not demonstrate any case of concomitant two mutations in the BRCA1 gene (i.e. 185delAG and 5382insC) suggesting that this phenomenon, similar to a homozygote double mutation, never previously reported in the literature, could be non-compatible with life.

Our studies were able to accurately measure the prevalence of a double BRCA heterozygosity status. Nevertheless, neither were we able to calculate person-years of follow-up for our clinical service nor could we compare carriers and non-carriers for differences in ovarian cancer incidence.

With these limitations in mind, our data, together with data formerly published by others, suggest that the phenomena of double heterozygosity in Jewish populations is relatively rare and that other than a slightly younger age at occurrence of disease, double heterozygote women do not have significantly different clinical characteristics that require a change in the counseling process or in the follow-up measures or treatment strategy with the newly suggested poly (ADP-ribose) polymerase inhibitors.

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disclosure

The authors declare no conflict of interest.

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