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Short Communication

The frequency of the predominant Jewish mutations in *BRCA1* and *BRCA2* in unselected Ashkenazi colorectal cancer patients

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Summary It is presently unclear whether carriers of *BRCA1* mutations have an increased risk for colorectal cancer (CRC). To gain insight into this issue, 225 unselected Ashkenazi Jewish CRC patients were tested for the presence of the three common Jewish *BRCA1/2* germline mutations: 185delAG and 5382insC (*BRCA1*) and 6174delT (*BRCA2*). A total of four carriers was found (4/225, 1.78%). This frequency is similar to the estimated normal Ashkenazi population frequency, thus suggesting that these specific mutations do not contribute to CRC predisposition. © 2001 Cancer Research Campaign http://www.bjcancer.com

Keywords: Ashkenazi Jews; colorectal cancer, *BRCA1*; *BRCA2*; 185delAG; 5382insC; 617delT; inherited predisposition

The co-occurrence of breast cancer (BC) and colorectal cancer (CRC) has previously been documented (Phipps and Perry, 1989; Ford et al, 1994; Schoen et al, 1994; Slattery and Kerber, 1994; Olsen et al, 1999). Women with a history of BC were found to have an increased risk for developing subsequent CRC (Rozen et al, 1986; Schoen et al, 1994). Such an association between BC and CRC could arise due to a genetic predisposition (Slattery and Kerber, 1994; Stoll, 1998). Several lines of evidence point to a possible contribution of mutations within the inherited BC susceptibility gene, *BRCA1*, to CRC pathogenesis: allelic losses at the *BRCA1* locus, putatively targeting this tumour suppressor gene, have been detected in almost 50% of sporadic CRCs (Garcia-Patino et al, 1998); Individuals within *BRCA1*-linked families have an increased risk for developing CRC – the relative risk of *BRCA1* mutation carriers (by haplotype analysis) for CRC was found to be 4.11 (Ford et al, 1994) and the risk for developing CRC in relatives of familial BC patients is increased over that of the general population (Phipps and Perry, 1989; Slattery and Kerber, 1994; Burke et al, 1997; Olsen et al, 1999). However, the increased risk for developing CRC in patients with familial BC is not uniformly reported by all investigators (Anderson and Badzioch, 1993; Lin et al, 1999). A high carrier rate of *BRCA1/2* families in a defined population permits a comparison of mutation frequencies between affected CRC individuals and the general population.

Among Ashkenazi (East European) Jews, three mutations in the *BRCA1* and *BRCA2* genes, account for the majority of inherited BC predisposition: 185delAG and 5382insC (*BRCA1*) and 6174delT (*BRCA2*). Furthermore, these mutations occur at a rate of about 2.5% among the general Jewish Ashkenazi population (Struewing et al, 1995, 1997; Roa et al, 1996; Fodor et al, 1998). These facts and the lack of conclusive evidence for an increased CRC risk in BC families, prompted us to directly analyse the relative contribution of these mutations to the pathogenesis of CRC in Ashkenazi Jews.

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MATERIALS AND METHODS

Subjects

225 consecutive Ashkenazi CRC patients were included in the study: 125 men and 100 women. The patients were diagnosed at the Sheba and Rabin Medical Centers and had pathologically confirmed tumours. The Ashkenazi descent was ascertained at least three generations back. The mean age at diagnosis was 65.3 ± 17.2 years, and the mean age at the time of study was 73.5 ± 11.0 years.

The study was approved by the Institutional Review Board at both medical centres. All participants signed a written informed consent, and a detailed questionnaire, with special emphasis on cancer family history was filled out.

Molecular analysis

DNA was extracted from peripheral blood leukocytes using standard techniques and analysis for the three predominant mutations was performed using PCR and restriction fragment length polymorphism, as previously described (Rohlfs et al, 1997) and adopted by us (Bruchim Bar-Sade et al, 1998).

Statistical analysis

Carrier frequency rates were compared between the CRC study group and published data regarding the general Ashkenazi population, using Fisher's Exact Test.

RESULTS

Overall, 4 out of the 225 patients tested (1.78%) were *BRCA1/BRCA2* mutation carriers. The carriers consisted of two

Table 1 Clinopathological data of *BRCA1/2* mutation carriers

Patient	Sex	BC personal diagnosis age	BC diagnosis age in 1st degree relative	CRC diagnosis age	*BRCA1/2* mutation status
C1	F	49	–	67	6174delT
C2	F	62	–	85	6174delT
C3	M	–	32	72	185delAG
C4[a]	M	–	–	75	5382insC

[a]Patient C4's mother was diagnosed with endometrial cancer, diagnosis age unknown.

Table 2 Carrier frequency of the three predominant Jewish *BRCA1/2* mutations

Mutation	CRC patients	Healthy controls (Struewing et al, 1997)	*P* value[a]
185delAG	1/225 (0.44%)	41/5318 (0.77%)	NS
5382insC	1/225 (0.44%)	20/5318 (0.38%)	NS
6174delT	2/225 (0.88%)	59/5318 (1.11%)	NS
Total	4/225 (1.78%)	120/5318 (2.26%)	NS

[a]Statistical analysis using Fisher's Exact Test.

males and two females. One male patient was a 185delAG *BRCA1* mutation carrier (0.44%) and the other male a 5382insC *BRCA1* mutation carrier (0.44%). The two female patients (0.88%) harboured the 6174delT *BRCA2* mutation. Of note, 3 out of the 4 mutation carriers had either a personal or family history of BC. The relevant clinical data of these carrier individuals are shown in Table 1. The differences between the mutation carrier frequencies in this patient population were not statistically significant compared with those of the general population (Struewing et al, 1997), as calculated using Fisher's Exact Test (Table 2).

Among the remaining 98 non-carrier females with CRC, only one patient (1.02%) had a primary diagnosis of BC at age 52 years and a diagnosis of CRC 18 years later. 13 out of the 131 (9.92%) CRC patients, who completed the family history questionnaire, reported BC in a first degree family member. This rate is in concordance with the rates of BC in the general Jewish population (Bar-Chana et al, 1996).

DISCUSSION

Previous analysis of the three common Jewish *BRCA1/2* germline mutations in a large, unselected group of Jewish Asheknazi individuals did not find an increased risk for developing CRC among mutation carriers (Struewing et al, 1997). Lin et al reported that the lifetime risk for CRC in 32 American *BRCA1/2* families was similar to the risk in the general population (1999). Our results support these data by analysis of unselected CRC patients, and complement previous studies performed on individuals from high-risk families. Of note, had we excluded patients with personal or familial history of BC from the patient cohort as well as from the control group analysed, the lack of association between these mutations and CRC would be even more striking. Taken together with the recent publications showing these specific mutations do not increase the risk for prostate cancer in this ethnic group (Lehrer et al, 1998; Hubert et al, 1999; Vazina et al, 2000), we can conclude that the predominant Ashkenazi Jewish *BRCA1* and *BRCA2* mutations do not contribute to the pathogenesis of CRC. Thus, it seems that the two major indications for performing *BRCA1/2* genetic testing in men are the personal risk for developing BC (Struewing et al, 1999) and the risk of transmitting the mutated alleles to their daughters.

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