Prevalence of Breast and Colorectal Cancer in Ashkenazi Jewish Carriers of Fanconi Anemia and Bloom Syndrome

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Abstract

Background: Fanconi anemia complementation group C and Bloom syndrome, rare autosomal recessive disorders marked by chromosome instability, are especially prevalent in the Ashkenazi* Jewish community. A single predominant mutation for each has been reported in Ashkenazi Jews: c.711+4A→T (IVS4 +4 A→T) in *FACC* and *BLM*^{Ash} in Bloom syndrome. Individuals affected by either of these syndromes are characterized by susceptibility for developing malignancies, and we questioned whether heterozygote carriers have a similarly increased risk.

Objectives: To estimate the cancer rate among *FACC* and *BLM*^{Ash} carriers and their families over three previous generations in unselected Ashkenazi Jewish individuals.

Methods: We studied 42 *FACC* carriers, 28 *BLM*^{Ash} carriers and 43 controls. The control subjects were Ashkenazi Jews participating in our prenatal genetic screening program who tested negative for *FACC* and *BLM*^{Ash}. All subjects filled out a questionnaire regarding their own and a three-generation family history of cancer. The prevalence rates of cancer among relatives of *FACC*, *BLM*^{Ash} and controls were computed and compared using the chi-square test.

Results: In 463 relatives of *FACC* carriers, 45 malignancies were reported (9.7%) including 10 breast (2.2%) and 13 colon cancers (2.8%). Among 326 relatives of *BLM*^{Ash} carriers there were 30 malignancies (9.2%) including 7 breast (2.1%) and 4 colon cancers (1.2%). Controls consisted of 503 family members with 63 reported malignancies (12.5%) including 11 breast (2.2%) and 11 colon cancers (2.2%).

Conclusions: We found no significantly increased prevalence of malignancies among carriers in at least three generations compared to the controls.

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Fanconi anemia and Bloom syndrome are rare autosomal recessive disorders, and are two of several genetic conditions marked by chromosome instability [1,2]. Bloom syndrome (OMIM# 210900) and a specific type of Fanconi anemia, Fanconi anemia complementation group C (OMIM# 227645), are especially prevalent in the Ashkenazi Jewish community. In order to estimate the heterozygote frequencies of FACC and Bloom syndrome in Israel, Peleg et al. [3] studied more than 4000 subjects. They estimated that in Israeli Jews of Ashkenazi origin the carrier rate of *FACC* is 1:92 and of Bloom syndrome 1:111 [3]. A study carried out among the Ashkenazi Jewish population in New York found the Bloom syndrome mutation in 5 of 1155 individuals, yielding a frequency of 1:231 [4].

Fanconi anemia is a severe disease characterized by growth retardation, congenital abnormalities and progressive bone marrow failure. Its molecular basis involves defective recombination leading to chromosomal instability and a tendency toward the development of malignancies, mostly leukemias and squamous cell carcinomas, usually of the head and neck. There are at least 12 complementation groups with 11 identified genes [5,6]; the *FACC* gene has been mapped to chromosome 9q22.3. A single predominant mutation, c.711+4A→T (commonly known as IVS4 +4 A→T), has been reported in Ashkenazi Jews.

Bloom syndrome is characterized by growth failure, facial erythema, immune deficiencies, and susceptibility to various types of cancer. The Bloom syndrome gene, *BLM*, has been mapped to 15q26.1 and its product was found to encode a RecQ DNA helicase. The role of the BLM protein was shown to involve recognition and prevention of illegitimate recombination. When the BLM protein is defective, as in Bloom syndrome, it is associated with the early occurrence of various cancers [7]. A single predominant frameshift mutation in exon 10 of the *BLM* gene has been reported in Ashkenazi Jews: 2281delATCTGAinsTAGATTC (*BLM*^{Ash}).

Since patients with Fanconi anemia and Bloom syndrome who are homozygous mutation carriers have a well-documented increased risk of developing malignancies, the question was raised as to whether carriers, who are heterozygous for *FACC* or *BLM*^{Ash}, also have an increased risk. The aim of our study was to estimate the cancer rate, particularly for breast and colon cancer, among *BLM*^{Ash} and *FACC* heterozygotes and their families over three previous generations in unselected individuals.

Patients and Methods

We studied 42 carriers of *FACC*, 28 carriers of *BLM*^{Ash}, and 43 controls, all of Ashkenazi Jewish ancestry, in order to estimate the

* Jews of East European origin
FACC = Fanconi anemia complementation group C

relative risk of colorectal cancer, breast cancer and other types of malignancies in their families. All 113 individuals included in our study were participants in our genetic screening program. This program, which has been running for many years, is aimed at detecting carriers of various genetic disorders among the general Israeli population, and most of the participants are women who undergo the tests as part of their prenatal workup. The tests recommended depend on the ethnic origin of both spouses since certain diseases are only prevalent in specific ethnic groups.

Between the years 1995 and 2002 we contacted all individuals who were found to be carriers of either *FACC* or *BLM*^{Ash}, as well as, during 2002, a group of controls who tested negative for these disorders. Each individual was asked to fill out a questionnaire about their colorectal history and their extended, three-generation family's cancer history (including siblings, parents, uncles, aunts and grandparents) as well as the total number of relatives in the family. If such information was unknown to them during the initial interview they were asked to call back with more details and to confirm their information. This information was not validated against medical records.

The subjects were first-degree and second-degree family members of heterozygotes for the *FACC* and *BLM*^{Ash} mutations. Since this was a retrospective study, the relatives of the carriers were not tested nor were they asked whether they had undergone such testing. The control group consisted of first-degree and second-degree family members of individuals who tested negative for these mutations [Tables 1-3].

The prevalence rates of cancer among relatives of *FACC* and *BLM*^{Ash} carriers were calculated and compared to the prevalence in relatives of controls using the chi-square test. We used the polymerase chain reaction, restriction analysis and gel electrophoresis to identify mutations in the relevant genomic fragments as described elsewhere [8]. The Human Subjects Committee of the Rabin Medical Center approved the study protocol and all participants gave informed consent.

Table 1. Characteristics of the subjects in the *FACC* carrier, *BLM*^{Ash} carrier and control groups

	FACC	*BLM*^{Ash}	Control	*P*
No. of probands	42	28	43	
Age (yrs) (mean ± SD)*	29 ± 4	31 ± 5	31 ± 4	0.02
Female N (%)**	34 (85%)	22 (81%)	36 (88%)	0.70
No. of first-degree relatives	157	116	180	
Total no. of parents	84	56	86	
Total no. of siblings	73	60	94	
No. of siblings per family median (Q1, Q3)	2 (1,2)	2 (1,3)	2 (2,3)	0.07
No. of second-degree relatives	306	210	323	
Total no. of grandparents	168	112	172	
Total no. of aunts/uncles	138	98	151	
Total no. of first and second-degree relatives	463	326	503	

* Age not available for 1 *BLM*^{Ash}, 5 controls

** Gender not available for 1 *BLM*^{Ash}, 2 *FACC*, 2 controls

Results

We analyzed the family data of 42 carriers of *FACC*, 28 carriers of *BLM*^{Ash}, and 43 controls, all of Ashkenazi Jewish ancestry. For Fanconi anemia, this yielded 463 individuals (mean 11.2 ± 2.6 relatives per carrier), for Bloom syndrome 326 individuals (11.6 ± 2.9 relatives per carrier), and for the control group 503 individuals (11.7 ± 2.8 relatives per control). Table 1 details the characteristics of the subjects in the three groups, Table 2 shows the distribution of the types of malignancies among first and second-degree relatives, and Table 3 details the prevalence rates of cancer in first and second-degree relatives of *FACC* and *BLM*^{Ash} carriers compared to controls.

The risk for being a carrier is 50% among first-degree relatives and 25% among second-degree relatives. Table 2 details the types of malignancies found in each of the groups. In the group of first-degree relatives of *FACC* carriers, there were in total four individuals with cancer (2.6%), compared to first-degree relatives of controls with a total of 18 individuals with malignancies (10%) ($P = 0.01$), including one mother with two types of cancer (lung and brain) and one mother with three types of cancer (breast, leukemia and liver). In the group of first-degree relatives of *BLM*^{Ash} carriers there were in total 11 individuals with cancer (9.5%) (one of the mothers had two types of cancer, breast and melanoma), compared with 18 in first-degree relatives of controls (10%) ($P = 1.0$). Among second-degree relatives of the *FACC* carriers, 41 individuals with cancer were reported (13.4%), including one grandmother with three types of cancer (breast, colon and uterus), compared to 45 reported cancer cases among second-degree relatives of controls (13.9%) ($P = 0.94$). Among second-degree relatives of *BLM*^{Ash} carriers 19 cancer cases were reported (9%), compared to 45 second-degree relatives of controls (13.9%) ($P = 0.12$).

Discussion

The increased risk of malignancy in patients with Fanconi anemia and Bloom syndrome is well established [9]. The debate in the literature is whether there is also an increased risk for malignancy among heterozygotes. In 1980 Swift and co-authors [10] studied the prevalence of cancer in the blood relatives of Fanconi anemia patients and found that there were fewer than expected deaths from leukemia. Although there were more deaths and cases of bladder, stomach and breast cancer among blood relatives than expected, the differences were not statistically significant. In 2000 Rischewski et al. [11] screened DNA from pediatric patients with myelodysplastic syndrome, chronic myelomonocytic leukemia, juvenile myelomonocytic leukemia or acute myeloid leukemia for mutations in the *FANCA*, *FANCC* and *FANCG* genes. They found a novel heterozygous frameshift mutation, 377-378delGA, in the *FANCC* gene in two siblings who both suffered from T cell acute lymphoblastic leukemia, with subsequent myelodysplastic syndrome transforming to acute myeloid leukemia in one of them. The authors speculated that the findings in this family support the hypothesis that there is an increased risk of developing malignancies among heterozygous carriers of *FANC* mutations. However, an obvious criticism is the danger of basing conclu-

Table 2. Distribution of the types of malignancies among first and second-degree relatives

	N	With cancer N (%)	Breast	Colon	Brain	Leuk	Lung	Ovary	Prostate	Melanoma	Liver	Other
FACC												
1st degree – total:	157	4 (2.6%)	1	0	0	0	1	0	0	0	0	2
Parents	84	4 (4.8%)	1	0	0	0	1	0	0	0	0	1 (thymus), 1 (testis)
Siblings	73	0 (0%)	0	0	0	0	0	0	0	0	0	0
2nd degree – total:	306	41 (13.4%)	9	13	3	3	0	2	0	1	2	10
Grandparents	168	33 (19.6%)*	5	12	1	3	0	2	0	1	2	1 (nasopharynx), 2 (uterus), 2 (bladder) 1 (myelofibroma), 3 (bone)
Aunts/uncles	138	8 (5.8%)	4	1	2	0	0	0	0	0	0	1 (lymphoma)
***BLM*^{Ash}**												
1st degree – total:	116	11 (9.5%)*	3	0	0	1	0	0	2	1	0	5
Parents	56	10 (17.9%)	3	0	0	1	0	0	2	1	0	2 (lymphoma), 1 (local skin), 1 (kidney)
Siblings	60	1 (1.7%)	0	0	0	0	0	0	0	0	0	1 (thyroid)
2nd degree – total:	210	19 (9.0%)	4	4	2	0	1	0	2	0	0	6
Grandparents	112	11 (9.8%)	2	1	1	0	0	0	2	0	0	1 (uterus), 2 (stomach), 1 (bone) 1 (not known)
Aunts/uncles	98	8 (8.2%)	2	3	1	0	1	0	0	0	0	1 (stomach)
Controls												
1st degree – total:	180	18 (10.0%)	4	2	2	1	3	1	2	1	1	4
Parents	86	16 (18.6%)*	4	2	2	1	3	1	2	0	1	1 (thyroid), 1 (pancreas), 1 (not known)
Siblings	94	2 (2.1%)	0	0	0	0	0	0	0	1	0	1 (testis)
2nd degree – total:	323	45 (13.9%)	7	9	0	4	2	4	1	3	2	13
Grandparents	172	35 (20.4%)	4	8	0	3	2	4	1	0	2	1 (bladder), 2 (lymphoma), 1 (stomach) 1 (pancreas), 1 (disseminated carcinoma), 5 (not known)
Aunts/uncles	151	10 (6.6%)	3	1	0	1	0	0	0	3	0	1 (nasopharynx), 1 (uterus)
TOTAL			28	28	7	9	7	7	7	6	5	40

* The grandmother of one *FACC* carrier and the mother of one control each had three types of malignancy; the mother of one *BLM*^{Ash} carrier and the mother of one control each had two types of malignancy.

sions on the findings in one specific family whose predisposition to cancer could well be due to other causes. Another line of supportive evidence for the possibility that heterozygote carriers are at an increased risk comes from *in vitro* studies. In 2001, Barquinero and team [12] investigated the mean frequencies of bleomycin-induced chromatid breaks from three FA heterozygotes and 11 controls and found a significantly higher number of chromatid breaks in the FA heterozygotes ($P < 0.001$). Djuzenova et al. [13] exposed peripheral blood mononuclear cells from FA patients and carriers to X-rays and found that the cells of both patients and carriers showed uniformly high initial DNA damage rates.

As in Fanconi anemia, several investigators have carried out *in vitro* and epidemiological studies on *BLM* carriers to test the notion of increased cancer risk in heterozygous carriers. In 2002, Goss and collaborators [14] conducted a study on mice heterozygous for a targeted null mutation of Blm, the murine homolog of *BLM*, and found that on exposure to a viral carcinogen they developed lymphoma earlier than their wild-type littermates did. In addition, Gruber et al. [15] in 2002 genotyped 1244 cases of colorectal cancer and 1839 controls, all of Ashkenazi Jewish ancestry from Israel and New York, and found that those with colorectal cancer were more than twice as likely to carry *BLM*^{Ash} than the controls without this cancer [15]. However, in 2003, Cleary et al. [16] tested 2333 Jewish individuals of Ashkenazi origin, including those with a personal or family history of cancer (subjects) and those without (controls) [16]. Of these, 21 (0.9%) were carriers of *BLM*^{Ash}, and there was no significant difference between the *BLM*^{Ash} allele frequency in individuals with a personal or family history of cancer and in controls.

A study by Koren-Michowitz and colleagues [17] in 2005 investigated whether the co-inheritance of *BRCA1* and *BRCA2* mutations with Fanconi anemia and Bloom syndrome mutations in the Ashkenazi Jewish population might play a role in risk modification for cancer development [17]. They found that there was an increased prevalence of both *FACC* and *BLM*^{Ash} carriers among *BRCA1* and *BRCA2* mutation carriers compared with the general Ashkenazi population, but they did not find a statistically

FA = Fanconi anemia

Table 3. Prevalence rates of cancer in first and second-degree relatives of *FACC* and *BLM*^{Ash} carriers compared to controls

	Relatives of *FACC* carriers (%)	Relatives of *BLM*^{Ash} carriers (%)	Controls (%)	*FACC* carriers/ controls *(P)*	*BLM*^{Ash} carriers/ controls *(P)*
First-degree – total	2.6	9.5	10.0	0.01	1.00
Parents	4.8	17.9	18.6	0.01	1.00
Siblings	0	1.7	1.7	–	–
Second-degree – total	13.4	9.0	13.9	0.94	0.12
Grandparents	19.6	9.8	20.4	0.98	0.03
Aunt/uncle	5.8	8.2	6.6	0.96	0.83

significant effect of the co-inheritance on cancer prevalence, type of cancer, or age of onset of the cancer. This study highlights the possible role of other genetic modifying factors that may influence the risk for cancer development in carriers of known malignancy-related syndromes [17].

In the present study, no increased risk of familial clustering of malignancies was found in *FACC* and *BLM*^{Ash} mutation carriers going back three generations compared with non-carrier controls. In fact, among the families of the Fanconi anemia carriers we found statistically significantly fewer cancer cases in the first-degree relatives compared with controls. This is possibly due to the small sample size or multiple comparisons, and due to the younger age of the *FACC* carriers [Table 1]. In the families of the Bloom syndrome carriers, we found statistically significantly fewer cancer cases among the second-degree relatives compared to controls, again, possibly due to the small sample size or multiple comparisons.

To the best of our knowledge, this is the first study to investigate the risk for malignancy in carriers of *BLM*^{Ash}. Our study is also unique in that it is the only one to test healthy individuals on a random basis. This study did not show an increased risk for cancer in families of carriers of germline mutations in both *FACC* and *BLM*^{Ash}. However, given the limited sample size, only a larger prospective study could facilitate establishing any putative elevated cancer risk among *FACC* and *BLM*^{Ash} carriers.

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