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The Jewish Ashkenazi Founder Mutations in the BRCA1/BRCA2 Genes Are Not Found at an Increased Frequency in Ashkenazi Patients with Prostate Cancer

To the Editor:

BRCA1 and BRCA2, the predisposing genes for breast cancer (BC) and ovarian cancer (OC), have been suggested to increase the risk of prostate cancer (PrC) in male carriers (Ford et al. 1994; Thorlacius et al. 1996; Struewing et al. 1997); however, no direct evidence exists to confirm this hypothesis. A population with a high carrier frequency of BRCA1 and BRCA2 germinal mutations allows a direct approach to studying the role BRCA1 and BRCA2 play in the development of PrC; if germinal mutations in BRCA1 and BRCA2 increase the risk of PrC in carriers, it is to be expected that the carrier frequency in PrC patients will be higher than in the general population, as was demonstrated in female patients diagnosed with BC and OC (Ford et al. 1995; Claus et al. 1996, Abeliovich et al. 1997).

In the Ashkenazi Jewish population, three founder mutations, 185delAG and 5382insC in the BRCA1 gene and 6174delT in the BRCA2 gene, exist at a high frequency (2.5%) (Struewing et al. 1995; Oddoux et al. 1996; Roa et al. 1996; Fodor et al. 1998). To assess the contribution of the BRCA1/BRCA2 germinal mutations to PrC morbidity, we analyzed the Ashkenazi founder mutations in two groups (with the same age distribution) of Ashkenazi men, a group of unselected PrC patients, and a control group of men with no history of cancer. The study was designed around the fact that, in families known to segregate BRCA1/BRCA2 mutations, men with PrC were noted sporadically. It was thus assumed that, if BRCA1 and BRCA2 play a role in the development of PrC, they do so as risk modifiers rather than as major dominant genes, and therefore will not be confined to familial cases.

Patients diagnosed with adenocarcinoma of the prostate (n = 87) were recruited from the oncology outpatient clinic at Sharett Institute, Hadassah Hebrew University Hospital, with no preselection. The patients signed an informed-consent form approved by the hospital's ethics committee. Each patient was interviewed regarding his family history. Clinical and pathological records were the sources of the clinical data.

The control group included 87 healthy men with no history of cancer. These men were approached in Jerusalem-area homes for the elderly and were asked to participate in the study; if they agreed, they signed an informed-consent form. Their blood samples were kept anonymous, labeled only with the patients' ages and origins (table 1). The median age was 71 years at the time of diagnosis for the patients with PrC and 72 years at the time of blood sampling for the control group (table 2). The mutations were analyzed as described elsewhere (Abeliovich et al. 1997).

The risk of developing PrC is age-dependent and is determined by differential exposure to environmental factors. In addition, positive family history is a major risk factor for developing PrC at an early age (Steinberg et al. 1990; Spitz et al. 1991; Whittemore et al. 1995). It is assumed that ~10% of all cases of PrC and half of the cases diagnosed at an early age (<60 years) are dominantly inherited. Linkage analyses in families with multiple cases of PrC pointed to a PrC-susceptibility gene (or group of genes) on chromosome 1 (Smith et al. 1996; Grönberg et al. 1997*a*; Berthon et al. 1998; Schaid et al. 1998), and, recently, an X-linked gene was suggested (Xu et al. 1998). It can be argued that BRCA1 and BRCA2 markedly reduce the age at onset of PrC and that therefore the effect of BRCA1/BRCA2 will be shown only in patients diagnosed with PrC at age <60 years, whereas in our study only five patients were ascertained in this age group. However, since 2.5% of Ashkenazi males are BRCA1/BRCA2 carriers, it would be expected that an excess of Ashkenazi men will develop PrC at age <60 years. The stratification of the ages

Table 1

Study Group of Ashkenazi Patients with PrC and Control Group: Age at Diagnosis, Cancer History, and the Ashkenazi BRCA1/BRCA2 Founder Mutations

Group	No. of Subjects Diagnosed or Tested at Age (in Years)						Group Total
	<50	50–59	60–69	70–79	>80	Unknown	
All subjects[a]	1	9	72	142	29	…	253
PrC study group	1	4	36	38	3	5	87
Carriers	…	1[b]	1[c]	1[d]	…	…	3
Carriers with second primary tumor[e]	…	1	1	…	…	…	2
Carriers with cancer in family	…	…	1	…	…	…	1
Noncarriers with second primary tumor[f]	…	…	4	4	…	1	9
Noncarriers with cancer in family[g]	…	2	10	11	1	2	26
Control group	…	3	27	31	26	3	87
Carriers	…	2[h]	…	1[i]	…	…	…

[a] Total number of Ashkenazi patients treated in Sharett Oncology Institute from January 1991 to July 1997.
[b] Patient A, carrying mutation 185delAG.
[c] Patient B, carrying mutation 6174delT.
[d] Patient C, carrying mutation 185delAG.
[e] Patient A had chronic lymphocytic leukemia; patient B had BC at age 59 years.
[f] Second primary tumors included melanoma ($n = 3$) and tumors of the bladder ($n = 2$), lung ($n = 1$), rectum ($n = 2$), and kidney and colon in the same patient.
[g] Six patients had first-degree relatives with PrC; eight patients had first-degree relatives with BC, including one male relative.
[h] Carriers of mutation 185delAG.
[i] Carrier of mutation 6174delT.

at diagnosis in the study group was similar to that of PrC patients in Israel, and only rarely are patients diagnosed before age 50 years (Israel Cancer Registry, 1994). The data of Struewing et al. (1997) also support the view that there is no excess of Ashkenazi patients with PrC diagnosed at age <50 years. They estimated the risk of cancer among relatives of Ashkenazi carriers of BRCA1 and BRCA2, which for PrC was 16% (95% confidence interval [CI] 4%–30%) by age 70 years; by age 80 years the risk increased to 39%. Interestingly, in the same study (Struewing et al. 1997), the risk of OC was 16% by age 70 years (95% CI 6%–28%), similar to that of PrC. It should be emphasized that, although BRCA1/BRCA2 are major dominant genes in BC and in OC and although carriers tend to develop those cancers at a young age, 18% of the female patients diagnosed at age ⩾50 years with BC or OC were carriers of BRCA1 or BRCA2—8% of the BC patients and 66% of the OC patients (Abeliovich et al. 1997).

Three patients in the study group were identified as mutation carriers: patients A and C with 185delAG (BRCA1) and patient B with 6174delT (BRCA2). In the control group, three individuals were identified as carriers, two with 185delAG and one with 6174delT (table 1).

Two of the three carrier patients had second primary tumors: CLL (chronic lymphocytic leukemia) in patient A, and breast cancer in patient B. Among the noncarrier patients, 9 (11%) of 84 had a second primary tumor (including one patient with two second primary tumors).

A history of cancer in first-degree relatives was noted in patient B: his sister had BC, his father had PrC, and his son had testicular cancer. The two carrier patients, A and C, did not have positive family histories (the close relatives of patient A died in the Holocaust). Cancer history in first-degree relatives was noted in 26 (31%) of the 84 patients (table 1); in 5 of these patients the cancer was PrC, and the mothers of 4 had BC (both the mother and the daughter of one of these 4 had BC). The father of 1 patient had BC; the sisters of 2 others had BC; and the mother of 1 other had OC.

The clinicopathological data of the carrier and noncarrier patients is given in table 2. The carrier patients

Table 2

Clinicopathological Characteristics of Patients

Stage (No. of Patients)	PSA[a] at Diagnosis (No. of Patients)	Gleason Score (No. of Patients)
Noncarrier patients		
A (5)	5.9 (3)	5.4 (5)
B (35)	13.6 (28)	5.9 (31)
C (27)	32.8 (21)	6.2 (24)
D (12)	37.4 (10)	7.6 (5)
Carrier patients		
B (patient A[b])	60	>8
B (patient B[c])	47	8
B (patient C[b])	60	7

[a] In mg/ml.
[b] Carrier of mutation 185delAG.
[c] Carrier of mutation 6174delT.

were diagnosed at ages 57, 62, and 73 years (average 64 years). The average level of prostate serum antigen (PSA) in the carrier patients was 55.8 mg/ml, higher than the average (23.6) in noncarrier patients at all stages; the difference in the PSA level was highly significant ($\chi^2 > 30$). The three carrier patients were diagnosed at stage B with Gleason scores of 7, 8, and >8, higher than the average (5.9) for the noncarrier patients at stage B and similar to the average at stage D. The clinicopathological records of the patients indicated that the tumors in the three carriers were highly proliferative. This may suggest that mutations in BRCA1 and BRCA2 may have some role in the progression of the disease. A similar observation was made of PrC in patients who belong to HPC1-linked families (Grönberg et al. 1997*b*) and in BRCA1-associated breast cancers (Eisinger et al. 1996; Marcus et al. 1996; Blackwood and Weber 1998; Robson et al. 1998). However, this conclusion is based on three patients and should be confirmed in a larger number of patients.

The frequency of carriers in the study group of PrC patients and in the group of healthy men was 3.4% (95% CI 1.48%–5.4%), which is within the range of the population frequency (2.5%) (Fodor et al. 1998). In order to detect a minor difference between the two groups, a much larger sample was needed. Instead, we chose a different approach in which we calculated the expected percentage of carriers of BRCA1/BRCA2 founder mutations among the PrC patients, on the basis of the existent risk figures: 16% by age 70 years and 39% by age 80 years (Struewing et al. 1997). Assuming that we follow Ashkenazi men from age 50 years through age 80 years, we further assumed that the rate of carriers is 2.5% and that among the carriers the average risk of developing PrC prior to age 80 years is ~20%. We would then expect that every year 33 of 100,000 new Ashkenazi patients with PrC would be carriers of any of the BRCA1/BRCA2 founder mutations. Israeli data show that the number of new cases among Ashkenazi men at this age (50–80 years), is ~260 in 100,000 (Israel Cancer Registry, 1994); hence the carriers would be ~13% of the patients (33/260). We had 87 patients, and therefore expected 11 carriers in our study group, but observed 3. The difference between the expected and observed result is highly significant ($P < .0005$ in the exact-binomial test). The size of the sample enables a power of $\geqslant$80% for detecting a difference in carriers of 2.5% in the control group and at least 12.5% in the patients group. It is interesting to note that the strong association found among Israeli females between ethnic origin and breast cancer is not evident for prostate cancer. The age-standardized rate of breast cancer among Jewish women born in Europe or America (i.e., having an Ashkenazi origin) is 1.57 times that of Jewish women born in North Africa (non-Ashkenazi origin), whereas the respective rate for men having prostate cancer is 0.9 (Israel Cancer Registry, 1994). The age-adjusted rate of PrC (per 100,000) in Israeli Jewish men by place of birth is 32.2 for those born in Europe and North America (Ashkenazi Jews), 32.5 for men born in Africa and Asia, and 43.5 for men born in Israel (Israel Cancer Registry, 1994). We therefore suggest that the contribution of BRCA1/BRCA2 germinal mutations to PrC morbidity is negligible. Our conclusion is in agreement with other studies in which PrC patients were tested directly (Langston et al. 1996; Johannesdottir et al. 1996; Wilkens et al. 1999) and with some of the epidemiological studies (Isaacs et al. 1995; McCahy et al. 1996). However, our conclusion contradicts other epidemiological studies (Arason et al. 1993; Ford et al. 1994; Thorlacius et al. 1996; Struewing et al. 1997), in which the data were based on information received about first-degree relatives of carriers, while the PrC patients themselves were not analyzed. It would be interesting to explore the possibility of other sources of variation, such as environmental factors that affect BRCA1/BRCA2 carriers to a greater extent than noncarriers and to which men in Israel are not exposed.

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An HFE Intronic Variant Promotes Misdiagnosis of Hereditary Hemochromatosis

To the Editor:

Hereditary hemochromatosis (HH; MIM 235200), an autosomal recessive disorder of iron metabolism, can result in numerous clinical complications and is estimated to affect ~1/300 individuals of northern European origin (Merryweather-Clarke et al. 1997). Two mutations—C282Y and H63D—that contribute to HH have been identified (Feder et al. 1996), and screening for the C282Y mutation, in particular, is routinely done to identify carriers and affected individuals. Biochemical markers indicate a relatively clear distinction between these two groups, with minimal clinical consequences for heterozygotes (Bulaj et al. 1996). We initiated screening for the C282Y mutation, using the primer sequences provided by Feder et al. (1996) and subsequent restriction digestion of PCR products (Jazwinska et al. 1996). Re-