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Frequency and Carrier Risk Associated with Common BRCA1 and BRCA2 Mutations in Ashkenazi Jewish Breast Cancer Patients

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Summary

Based on breast cancer families with multiple and/or early-onset cases, estimates of the lifetime risk of breast cancer in carriers of BRCA1 or BRCA2 mutations may be as high as 85%. The risk for individuals not selected for family history or other risk factors is uncertain. We determined the frequency of the common BRCA1 (185delAG and 5382insC) and BRCA2 (6174delT) mutations in a series of 268 anonymous Ashkenazi Jewish women with breast cancer, regardless of family history or age at onset. DNA was analyzed for the three mutations by allele-specific oligonucleotide hybridization. Eight patients (3.0%, 95% confidence interval [CI] 1.5%–5.8%) were heterozygous for the 185delAG mutation, two (0.75%, 95% CI 0.20–2.7) for the 5382insC mutation, and eight (3.0%, 95% CI 1.5–5.8) for the 6174delT mutation. The lifetime risk for breast cancer in Ashkenazi Jewish carriers of the BRCA1 185delAG or BRCA2 6174delT mutations was calculated to be 36%, approximately three times the overall risk for the general population (relative risk 2.9, 95% CI 1.5–5.8). For the 5382insC mutation, because of the low number of carriers found, further studies are necessary. The results differ markedly from previous estimates based on high-risk breast cancer families and are consistent with lower estimates derived from a recent population-based study in the Baltimore area. Thus, presymptomatic screening and counseling for these common mutations in Ashkenazi Jewish women not selected for family history of breast cancer should be reconsidered until the risk associated with these mutations is firmly established, especially since early diagnostic and preventive-treatment modalities are limited.

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Introduction

The findings of common mutations in the BRCA1 (185delAG) and BRCA2 (6174delT) genes in breast cancer families of Ashkenazi Jewish descent and of the high frequency of these mutations (~1%–1.5% each) among Ashkenazi Jewish individuals (Simard et al. 1994; Tonin et al. 1995; FitzGerald et al. 1996; Neuhausen et al 1996; Oddoux et al. 1996; Offit et al. 1996; Roa et al. 1996; Struewing et al. 1995; Tavtigian et al. 1996) have generated intense discussion concerning the relative ethical and medical merits and/or consequences of prospective screening in this population. Although such screening is now feasible, the risks and benefits of this approach remain uncertain because the lifetime risk of developing breast cancer among carriers of these mutations is unknown, particularly among women without a family history of breast cancer. Moreover, the absence of a mutation may lead to a false sense of reassurance. A high (92%) lifetime risk associated with breast cancer–predisposing genes, based on segregation analysis in families (age range 20–54 years), has been estimated (Claus et al. 1991), and a similarly high (85%) risk of the common BRCA1 and BRCA2 mutations has been reported in families with multiple affected first- and second-degree relatives with early-onset disease (Ford et al. 1994; Wooster et al. 1994; Easton et al. 1995; Stratton 1996; Shattuck-Eidens et al. 1997). However, relative risks (RRs) of the common BRCA1 and BRCA2 mutations in Ashkenazi Jewish families not selected for either the number of affected members or age at onset of breast cancer are uncertain; this precludes the ability to reliably inform carriers of their risk.

Previous studies determined the lifetime risk of the common BRCA1 185delAG and BRCA2 6174delT mutations in patients with early onset and/or extensive family history. It was estimated that, in the Ashkenazi Jewish population, 16% (Struewing et al. 1995), 20% (FitzGerald et al. 1996), or 22% (Offit et al. 1996) of breast cancer cases diagnosed at ages <50, <40, and <42 years, respectively, were attributable to the 185delAG mutation and that the RR of 185delAG carriers to develop breast

cancer at age <40 years was 27 times that of noncarriers (FitzGerald et al. 1996). Moreover, it was estimated that the lifetime risk (at age ⩽85 years) of carriers to develop breast cancer was ~85% (Ford et al. 1994; Easton et al. 1995). These studies provided estimates of age-related penetrance and attributable risks in early-onset patients or in patients with strong family histories. Recently, a population-based study of Ashkenazi Jewish volunteers in the Baltimore area estimated that the risk of breast cancer, by age 70 years, for carriers of one of the three common BRCA1 and BRCA2 mutations was 56%, significantly lower than previous estimates based on data from high-risk families (Struewing et al. 1997). However, estimates of risk from population-based studies of volunteers may introduce a selective bias toward those with a positive family history, leading to overestimations (Abeliovich et al. 1997; Struewing et al. 1997).

To assess the contributions of the common BRCA1 (185delAG and 5382insC) and BRCA2 (6174delT) mutations to the incidence of breast cancer in a breast cancer population of Ashkenazi Jewish descent, a study was undertaken to determine the frequency of these mutations in a consecutive series of 268 Ashkenazi Jewish female breast cancer patients who were not selected for family history or age at diagnosis. In addition, the population frequencies of the three common BRCA1 and BRCA2 mutations were determined in 1,715 Ashkenazi Jewish individuals from the same geographic area who requested prenatal carrier testing for genetic diseases that are more frequent among Ashkenazi Jews.

Subjects and Methods

Collection of Samples in the Ashkenazi Jewish Population

DNA samples from Ashkenazi Jewish men and women from the New York metropolitan area who were referred for prenatal carrier testing were archived, with informed consent, for use in other research studies. No identifiers were retained, and the samples were anonymous to investigators. The average age of this population was 35 years. Previous family- and cancer-history analysis did not reveal a personal history of breast cancer in any of these control individuals.

Collection of Samples from Ashkenazi Jewish Women with Breast Cancer

Clinical, family-history, and demographic information for a consecutive series of 298 self-identified Ashkenazi Jewish women with intraductal or infiltrating breast carcinoma who had had a biopsy, excision, or mastectomy at the Mount Sinai Medical Center, between 1986 and 1995, was entered into a database. Tissue blocks and stained slides of the primary breast carcinoma were obtained from 285 patients, and the histological features of the cancers were evaluated by two pathologists (I.J.B. and M.M.W.) and recorded in the database. After the tissue blocks were obtained, the original patient identifiers were removed, numerical identifiers were assigned, and the records and tissue blocks were distinguished by the new identifying numbers. Our institutional ethicist, acting as a third-party liaison, then assumed responsibility for maintaining the database. DNA results were communicated to the ethicist, who then entered the anonymous information into the database. In this way, all investigators were blinded to the combined data.

DNA Isolation

DNA was extracted from single 15-μm sections from paraffin-embedded archival tissue blocks (lymph node or breast) according to the dewaxing–Chelex-boiling method (Sepp et al. 1994). Amplifiable DNA was obtained from 268 of the 285 tissue blocks. Family histories regarding breast cancer were available in 262 of these cases.

Detection of the BRCA1 185delAG and 5382insC and BRCA2 6174delT Mutations by Allele-Specific Oligonucleotide (ASO) Hybridization

Triplex PCR was performed to amplify fragments of 250, 230, and 87 bp for the 185delAG, 5382insC, and 6174delT mutations, respectively. PCR primers for the 185delAG (Friedman et al. 1994), 5382insC (Gayther et al. 1996), and 6174delT (Neuhausen et al. 1996) mutations were "tagged" by a universal primer sequence, at the 5′ end, to facilitate simultaneous amplification (Shuber et al. 1995). The reaction contained 1 μM, 0.5 μM, and 0.75 μM of both primers for the 185delAG, 5382insC, and 6174delT mutations, respectively; 300 μM each dNTP; 2.5 mM $MgCl_2$; 1 × PCR buffer (Perkin-Elmer); 5 U *Taq* polymerase (Perkin-Elmer); and ~80 ng genomic DNA in a 50-μl reaction volume. PCR parameters were the same as those described by Shuber et al. (1995), except for a 20-s extension time.

For the detection of each mutation, 3-μl aliquots of the PCR products were blotted onto replicate membranes (8 × 12 cm) in a 96-well format by use of an automated pipetting workstation (Biomek 2000; Beckman Instruments). ASOs for the 185delAG (Struewing et al. 1996) and 5382insC mutations have been described elsewhere (Friedman et al. 1995). For the 6174delT mutation, the ASOs were wild type, 5′-ACA GCA AGT GGA AAA TC-3′, or mutation specific, 5′-ACA GCA AGG GAA AAT CT-3′. The membranes were hybridized for 1 h at 42°C with ~10^6 cpm of each end-labeled probe/ml, to detect the 185delAG and 6174delT mutations. For the 5382insC mutation, competitive hybridization was performed by addition of a 10-molar excess of the cold mutant and wild-type oligonucleotides along with the labeled wild-type and mutant probes,

respectively. The membranes were then washed sequentially in 6 × SSC for 10 min at room temperature and in 6 × SSC for 10 min at 45°C, followed by a wash at stringency (0.5 × SSC/0.1% SDS for 10 min at 45°C), and were then exposed to autoradiography (fig. 1). All positive results were confirmed by repeated analysis; in addition, some randomly selected positive cases were confirmed by DNA sequence analysis.

Statistical Analysis

The frequencies of mutations in the general population and in the breast cancer group were calculated from numbers of individuals in each group. The 95% confidence intervals (CIs) were determined by use of a binomial exact test. General population frequencies were compared with previous literature reports by use of Fisher's exact test. Odds ratios were estimated by use of the Mantel-Haentzel test. From SEER data (186,000 newly diagnosed breast cancers per year in the United States; Parker et al. 1997), the lifetime risk of breast cancer in the general population is calculated to be 12.5% (1 in 8), with the assumption of a life span of 85 years. The lifetime risk of breast cancer for the Ashkenazi Jewish population is not significantly different from that for the general population (Egan et al. 1996).

Carrier risk (R_C), RR, and attributable risk (AR) values were calculated by use of the following formulas: $R_C = C_{BC}R_G/F$, $RR = R_C/R_G$, and $AR(\%) = 100C_{BC}(RR - 1)/RR$, where C_{BC} is the proportion of mutation carriers among patients with breast cancer observed in the present study, R_G is the risk of breast cancer in the general population (.125), and F is the carrier frequency in the Ashkenazi Jewish population observed in the present study.

Results

Frequency of the Common BRCA1 and BRCA2 Mutations in the Ashkenazi Jewish Population

Among 1,715 anonymous DNA samples from a series of Ashkenazi Jewish men and women referred for prenatal carrier testing for Jewish genetic diseases, analysis for the 185delAG, 5382insC, and 6174delT mutations revealed Fs of 1.05%, 0.12%, and 1.05%, respectively (table 1). No individual carried more than one mutation. Thus, 2.22% of the individuals examined were heterozygous for one of the three mutations. These values for F were not significantly different from those previously reported for 185delAG (Roa et al. 1996; Struewing et al. 1996, 1997), 5382insC (Roa et al. 1996; Struewing et al. 1997), or 6174delT (Oddoux et al. 1996; Roa et al. 1996; Struewing et al. 1997), and the Fs obtained for each mutation by combining the data from the five studies were 0.92, 0.26, and 1.20, respectively (table 2).

Table 1

Mutation-Carrier Frequencies (F and C_{BC}) in Ashkenazi Jews

	Prenatal Screening Group (n = 1,715)		Breast Cancer Patients (n = 268)	
Mutation	No. (%) Positive	95% CI	No. (%) Positive	95% CI
185delAG	18 (1.05)	.7–1.8	8 (2.99)	1.5–5.8
6174delT	18 (1.05)	.7–1.8	8 (2.99)	1.5–5.8
5382insC	2 (.12)	0–.46	2 (.75)	.20–2.7

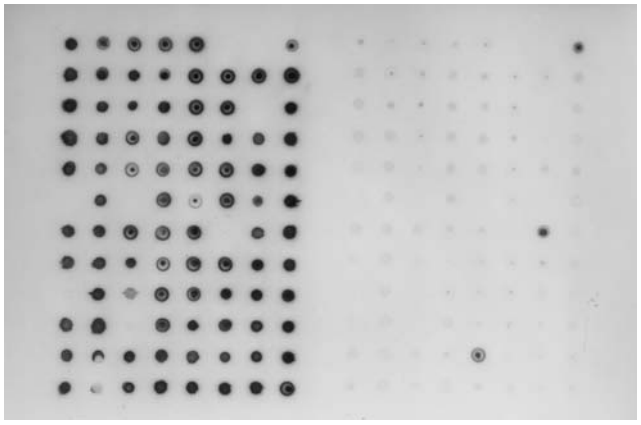

Figure 1 A representative dot-blot hybridization of the PCR products hybridized by allele-specific oligonucleotides complementary to the normal allele (*left panel*) and to the 6174delT mutant allele (*right panel*). A positive control is shown in the upper-right corner, preceded by a DNA blank; two patients were heterozygous for the mutation. Amplification failures were noted.

Frequency of the Common BRCA1 and BRCA2 Mutations in Ashkenazi Jewish Women with Breast Cancer

PCR-amplifiable DNA was obtained from a series of 268 archived pathological tissues from Ashkenazi Jewish female breast cancer patients who were not selected for age or family history. The average age at diagnosis was 58.7 years (range 35–90 years, SD 12.9 years); 19 women were age <42 years, 78 women were age 42–50 years, and 171 were age >50 years at diagnosis. Of the 262 women for whom family-history information was available, 162 reported negative family histories of breast cancer. A 36-year-old patient and a 48-year-old patient had both breast and ovarian cancer, and 11 patients had bilateral breast cancer. As shown in table 3, 18% of patients reported having a first-degree relative with breast cancer.

Eight (3.0%) of the 268 women studied were found to carry the 185delAG mutation, two (0.75%) carried the 5382insC mutation, and eight (3.0%) carried the 6174delT mutation (table 1). The family history, clinical

Table 2

Reported Carrier Frequencies for the Common BRCA1 and BRCA2 Mutations in the Ashkenazi Jewish Population

	185delAG			6174delT			5382insC		
STUDY	No. of Carriers	No. of People Screened	Carrier Frequency (%)	No. of Carriers	No. of People Screened	Carrier Frequency (%)	No. of Carriers	No. of People Screened	Carrier Frequency (%)
Struewing et al. (1995)	8	858	.93	...	...	...	...	...	...
Roa et al. (1996)	34	3,108	1.09	47	3,085	1.5	4	3,116	.13
Oddoux et al. (1996)	...	...	...	12	1,255	.96	...	...	...
Struewing et al. (1997)	41	5,318	.77	59	5,318	1.11	20	5,318	.38
Present study	18	1,715	1.05	18	1,715	1.05	2	1,715	.12
Overall	101	10,999	.92	136	11,373	1.20	26	10,149	.26

history, and pathological features of each of the 18 mutation carriers are given in table 4. Ten of the 18 mutation carriers were without a family history of breast cancer. Unexpectedly, only 3 of the 19 patients age <42 years carried a mutation, even though 11 of the remaining 16 patients had positive family histories of breast cancer. Five carriers were identified in the 42–50-year age group, and 10 were in the >50-year age group (table 5). A mutation was detected in 1 of the 11 patients who had bilateral cancer. Only 3 of the 19 patients who had at least two affected first- or second-degree relatives were found to carry a mutation. Notably, two patients who carried the 6174delT mutation had two affected relatives but developed breast cancer at ages 60 and 74 years, respectively.

The histopathological evaluation showed infiltrating ductal carcinoma in each of the 18 cases, with distinctive features in some. The majority (13 of 18) were poorly differentiated, as scored by modified Bloom-Scarf-Richardson criteria. Seven patients had metastatic carcinoma in axillary lymph nodes, 10 had negative lymph node findings, and 1 patient did not undergo axillary dissection. No distinctive histopathological characteristics were consistently observed in the tumors of carriers as compared with those of noncarriers.

Based on the observed F values and an assumed lifetime breast cancer risk of 85%, the expected number of both the BRCA1 185delAG and the BRCA2 6174delT mutation carriers among the 268 breast cancer patients was 18.0. However, for both mutations, only eight carriers were observed ($\chi^2 = 6.16$; $P = .013$). For the 5382insC mutation, the expected number of carriers (2.1) was similar to what was found (2). However, the wide CI (95% CI .002–.0268) for the proportion of 5382insC carriers among the patients, which is due to the low population frequency, indicated that further studies are required for risk estimation for this mutation (table 1).

Table 3

Family History of Breast Cancer among Ashkenazi Jewish Breast Cancer Patients and Mutation Carriers

No. of Affected Relatives, by Degree	No. of Patients	No. of Carriers
2 first	4	...
1 first , 2 second	2	...
1 first, 1 second, 1 third	3	1
1 first, 1 second	7	1
1 first, 1 third	5	1
1 first	26	...
2 second, 2 third	1	...
2 second	2	1
1 second, 1 third	6	1
1 second	34	2
2 third	1	...
1 third	19	1
Subtotal	110	8
Negative family history	152	10
Family history unavailable	6	...
Total	268	18

Discussion

Since the risk of breast cancer associated with the inheritance of the common BRCA1 and BRCA2 mutations in a population-based sample of Ashkenazi Jewish women is uncertain, the frequency of these mutations was determined in a series of Ashkenazi Jewish female breast cancer patients who were not selected for family history or age at onset. Of the 268 women studied, 42% had first-, second-, or third-degree relatives with breast cancer, but only 5 women had as many as three affected first- or second-degree relatives. Therefore, these women would not generally be classified as high risk (Hoskins et al. 1995), and the available risk estimates would not apply. The present study provided information on the frequency of the common BRCA1 185delAG and BRCA2 6174delT mutations in a group of Ashkenazi Jewish women considered to be at low or moderate risk because of the absence of a strong family history. These data permit the estimation of lifetime risks of breast cancer, which may be used for genetic counseling and decision making.

The RR of breast cancer among mutation carriers,

Table 4

Age at Onset and Family History of Breast Cancer among 18 Ashkenazi Jewish Carriers of Common BRCA1 and BRCA2 Mutations

Age at Onset (years)	Family History[a]
185delAG:	
44	+ (aunt, cousin)
67	− (ovarian cancer)
36	− (ovarian cancer)
56	+ (aunt, cousin)
44	+ (aunt)
68	−
56, 67	− (bilateral)
75	−
6174delT:	
60	+ (mother [60], cousin)
35	−
40	−
42	−
74	+ (sister, GM)
56	+ (GM, cousin)
63	− (bilateral)
46	+ (mother [64], maternal GM [36], maternal great GM)
5382insC:	
80	−
49	+ (GM, aunt)

[a] A plus sign (+) indicates a positive family history, and a minus sign (−) indicates a negative family history. GM = grandmother. Additional information regarding cancer status or affected family members (with age at onset, in years) appears in parentheses.

compared with noncarriers, was 2.90 (95% CI 1.46–5.78) for the 185delAG and 6174delT mutations, corresponding to a lifetime (age 85 years) risk of 36% for each mutation (table 6). For the 5382insC mutation, which has a population frequency of ~0.26%, a more extensive study must be performed. The finding of an equally low lifetime-risk value for the 6174delT mutation in this population-based setting is in contrast to previous speculations based on data obtained from high-risk families, which indicated that the penetrance of the 6174delT mutation was lower than that of the 185delAG mutation (Roa et al. 1996; Tonin et al. 1996).

The present study was conducted in a consecutive random series of 268 Ashkenazi Jewish breast cancer patients and thus eliminated the bias of ascertainment that may be reflected in the population-based study conducted by Struewing et al. (1997). In that study, 30% of the 288 survivors of breast cancer reported an affected first-degree relative, as opposed to 18% in the present study, which may be a more representative patient sample. However, the results of these two studies indicate that the R_C for these recurrent mutations is probably significantly less than previous estimates based on high-risk families.

Table 5

Germ-Line 185delAG, 5382insC, or 6174delT Mutations among Ashkenazi Jewish Breast Cancer Patients Stratified by Age at Onset

Age at Onset (years)	No. of Patients Studied	No. (%) of Mutation Carriers
<42	19	3 (16)
42–50	78	5 (6.4)
>50	171	10 (5.8)
Overall	268	18 (6.7)

For women at low-to-moderate risk for breast cancer, informed choices regarding prospective screening require information concerning the lifetime risks of breast cancer among women identified as mutation carriers. Clearly, the predictive value of positive and negative test results must be determined for informed decision making and genetic counseling. The predictive value of a negative test is 87.5%, whereas the predictive value of a positive test result is equal to R_C. Data obtained from this population indicate that the positive predictive value is 36% for both the 185delAG and the 6174delT mutations. In view of the low predictive value of positive mutation testing without strong family histories, together with the lack of effective primary and secondary breast cancer–prevention measures (reviewed by Stratton 1996), screening and counseling strategies may be best focused on high-risk women. Because of sample-size considerations, more extensive studies of nonselected groups of Ashkenazi Jewish breast cancer patients are necessary to confirm these results. Such findings would imply that, when presymptomatic testing for the common BRCA1 and BRCA2 mutations in the Ashkenazi Jewish population is considered, a clear distinction should be made between high-risk women (those with a strong family history and/or early-onset breast cancer) and women with low or moderate risk. In addition, more studies are necessary to estimate the breast cancer risk in individuals who carry the 5382insC mutation. Preliminary results from this study and others (Struewing et al. 1997) suggest that the lifetime risk associated with this mutation may be higher than the risks associated with the 185delAG or 6174delT mutations.

BRCA1 mutations have been associated with high-grade infiltrating carcinoma, as measured by its histological components of high proliferative activity, nuclear pleomorphism, and decreased tubule formation (Bignon et al. 1995; Eisinger et al. 1996; Marcus et al. 1996), as well as an excess of tumors with medullary features; however, survival in two reports was paradoxically not worsened despite the adverse prognostic features (Bignon et al. 1995; Marcus et al. 1996). BRCA2 mutations have reportedly been associated with tubulo-lobular group histology and a similarly favorable prognosis (Bignon et al. 1995). Although our study lacks sufficient numbers of mutation-positive cases to draw definitive

Table 6

R_C, RR, and AR Values Calculated from C_{BC} and F

Mutation	R_C	RR (95% CI)	AR
185delAG	.36	2.90 (1.46 –5.78)	1.95%
6174delT	.36	2.90 (1.46–5.78)	1.95%
5382insC	.81	6.44 (1.72–23.6)	.63%

NOTE.—A general population risk of .125 to develop breast cancer is assumed. See text for formulas used for these calculations.

conclusions, we found that both BRCA1 and BRCA2 mutation cases were associated with poorly differentiated tumors. In contrast to other authors, we found no excess of medullary features or tubulo-lobular histology in either group. Long-term follow-up information was not available because of the blinded nature of the study. Clearly the pathological characteristics and clinical outcome of these lesions are of great importance, deserving further investigations.

Although we could not show a correlation between the presence of the 185delAG or 6174delT mutations and clinical/pathological characteristics, the potential to evaluate genotype-phenotype relationships in groups of patients with the same mutation may yield important information regarding prognosis and possible treatment options. In addition, the lifetime risk values of 36% for both the 185delAG and 6174delT mutations indicate that other genetic or environmental factors interact with these mutant genes either to induce cancer or, alternatively, to protect carriers from developing breast cancer. The Ashkenazi Jewish population should provide an informed, cooperative, and relatively homogeneous population for further studies of the factors that influence the expression of breast cancer.

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