Prevalence and Penetrance of BRCA1 and BRCA2 Gene Mutations in Unselected Ashkenazi Jewish Women With Breast Cancer

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Background: **Approximately 2.0%–2.5% of Ashkenazi Jewish women carry one of three founding mutations in the BRCA1 and BRCA2 genes, and each mutation is associated with a high lifetime risk of invasive breast cancer. We investigated the extent to which these three mutations contribute to breast cancer incidence in the Ashkenazi Jewish population.** ***Methods:*** **We ascertained 457 Jewish women with prevalent cases of breast cancer who were unselected for age or family history of the disease; 412 of these women were tested for the three founder mutations (case patients). Control subjects consisted of 360 non-Jewish women with breast cancer (control patients) and 380 healthy Jewish women with no history of cancer (control subjects).** ***Results:*** **Mutations were found in 48 (11.7%) of 412 Jewish case patients. Forty-six of 48 mutations occurred in women with early-onset breast cancer (<50 years) or a history of ovarian or early-onset breast cancer in a first-, second-, or third-degree relative. The estimated penetrance to age 70 years for breast cancer was 59.9% for the BRCA1 gene mutations and 28.3% for the BRCA2 gene mutation. Compared with Jewish control subjects, the relative risk (RR) of breast cancer for first-degree relatives of mutation carriers was 5.16 (95% confidence interval [CI] = 3.14–8.48), but risk was also increased for relatives of noncarriers (RR = 1.66; 95% CI = 1.18–2.33). The RR of prostate cancer for first-degree relatives of Jewish case patients was 3.36 (95% CI = 1.49–7.56).** ***Conclusions:*** **Approximately 12% of breast cancers in the Ashkenazi Jewish population are attributable to mutations in the BRCA1 or BRCA2 gene. Genetic testing may be useful when Jewish women with breast cancer are diagnosed before age 50 years or have a close relative with ovarian or early-onset breast cancer. An association between breast and prostate cancers was observed in our study population. [J Natl Cancer Inst 1999; 91:1241–7]**

Ashkenazi Jews represent more than 90% of the 6 million Jews in the United States and Canada. The risk of breast cancer is greater for Jews than for non-Jews *(1,2)* and may be due to genetic or nongenetic factors. In a large case–control study *(3)*, the relative risk (RR) for breast cancer associated with Jewish ethnicity was 1.10 (95% confidence interval [CI] = 0.84–1.44). The RR, however, was higher for Jewish women who had a first-degree relative with breast cancer (RR = 1.95; 95% CI = 0.88–4.63) or who were diagnosed under the age of 50 years (RR = 1.55; 95% CI = 0.92–2.63). One possible explanation is a higher frequency of mutations in the breast cancer susceptibility genes BRCA1 and BRCA2 in the Jewish case patients. These mutations are present in 2.0%–2.5% of Ashkenazi Jewish men or women; this

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See "Notes" following "References."

frequency is approximately five times higher than that of the general population *(4–7)*.

To estimate the proportion of breast cancer cases among Jewish women with and without a family history of breast or ovarian cancer that is attributable to BRCA1 and BRCA2 gene mutations and to estimate the penetrance of these mutations, we performed genetic analysis of a hospital-based sample of 412 Jewish case patients with breast cancer. The cumulative risks of cancers of the breast, ovary, and other sites were estimated for the first-degree relatives of the Jewish case patients and compared with the cumulative risks of cancer among relatives of non-Jewish control patients with breast cancer and among relatives of healthy Jewish control subjects. We then evaluated the relative contribution of genetic and nongenetic risk factors to breast cancer incidence in the Jewish population.

SUBJECTS AND METHODS

Study Population

We ascertained 457 Jewish women with prevalent cases of breast cancer who were unselected for age or family history of the disease; 412 of these women were then tested for the three founder mutations. Control subjects were 360 non-Jewish women with breast cancer (control patients) and 380 healthy Jewish women with no history of cancer (control subjects).

Eligible subjects included all living Jewish women who had been diagnosed with invasive breast cancer before May 1, 1998, and who were followed at one of six oncology centers in Toronto or Montreal: Toronto-Sunnybrook Regional Cancer Centre, Mount Sinai Hospital, Women's College Hospital, The Toronto Hospital, North York General Hospital, and the Sir Mortimer B. Davis-Jewish General Hospital. The hospital lists of all living patients under follow-up for breast cancer (i.e., prevalent case patients) were reviewed. In some cases, the patient's religion was recorded in the medical record. In other cases, women of probable Jewish origin were identified presumptively by the patient's last name and physician knowledge. Jewish ancestry was confirmed by patient self-report at the time of interview. The diagnosis of invasive breast cancer was confirmed by review of the pathology record. Women who were Sephardic, who had converted to Judaism, or who were adopted were excluded.

A three-generation family history of cancer was obtained, either by telephone or in-person interview. All male and female first-degree relatives, including children, were ascertained, and their current age, age and cause of death (if deceased), and age and site of any cancer were recorded. Cases of breast and ovarian cancers in second- and third-degree relatives were also recorded. Pathologic confirmation was not routinely available for relatives. Additional epidemiologic data were obtained by questionnaire and included information on height, weight, reproductive history, use of oral contraceptives, and history of cigarette smoking.

After giving informed written consent, the Jewish patients with breast cancer were invited to undergo free of charge genetic testing for three founding mutations (185delAG, 5382insC, and 6174delT). Before giving a blood sample, all participants received genetic counseling. If requested by the patient, genetic test results were made available in the cancer genetics clinics of the participating hospitals, under existing counseling protocols. Forty-five women completed the questionnaire and family history interview but declined to enter the genetic testing protocol.

Two control populations were used. A group of 380 healthy Jewish women (control subjects) with no history of cancer, who were between the ages of 25 and 88 years, was recruited from two sources: 1) paid and unpaid workers (n = 120) from four U.S. hospitals (Cedar Sinai Hospital, Los Angeles, CA; Columbia Presbyterian Hospital Medical Center, New York, NY; Albert Einstein College of Medicine, Bronx, NY; and Yale University Medical Center, New Haven, CT) and one Canadian hospital (Sir Mortimer B. Davis-Jewish General Hospital) and 2) women (n = 260) from the membership lists of a Toronto synagogue and a local Jewish women's group. Control subjects were approached by a member of the study team at their workplace or through the mail. They were invited to participate in a study that dealt with breast and ovarian cancer risks, but they were not aware of the primary study goals. Control subjects were excluded if they had a history of breast or ovarian cancer, were Sephardic, had converted to Judaism, or were adopted. A second group contained 360 non-Jewish women with breast cancer (control patients), who were recruited from the outpatient breast cancer clinics of several of the participating hospitals. Both control groups provided details about their family history of cancer and completed the epidemiology questionnaire but were not offered genetic testing. Epidemiologic data were not included from Mount Sinai Hospital.

The study was approved by the institutional review boards of each participating hospital and the University of Toronto.

Laboratory Methods

DNA was extracted from peripheral blood lymphocytes from 412 Jewish case patients with breast cancer and was analyzed for the presence of two BRCA1 gene mutations (185delAG and 5382insC) and one BRCA2 gene mutation (6174delT). Mutation analysis was performed in four cancer genetics laboratories, using a range of accepted techniques, including heteroduplex analysis, direct sequencing, and allele-specific polymerase chain reaction *(4–11)*. Because the great majority of mutations reported to date in Jews have been either 185delAG or 5382insC in BRCA1 or 6174delT in BRCA2, the mutation analysis was confined to these three mutations.

Statistical Analysis

The frequency of the three common Jewish mutations was measured as the proportion of positive case patients among the total number of case patients. Proportions were estimated according to age of onset of the breast cancer and whether the women had a family history of breast or ovarian cancer.

The cumulative risk of breast or ovarian cancer was calculated for the first-degree female relatives (mother, sisters, and daughters) of the Jewish case patients with breast cancer from a life-table analysis. In this analysis, all first-degree female relatives were considered study subjects. The "exposed" cohort contained the first-degree relatives of the Jewish case patients with breast cancer; the "unexposed" groups contained the first-degree relatives of subjects in each control group. The cumulative risks were calculated for first-degree relatives of Jewish case patients with breast cancer who carried mutations, Jewish case patients with breast cancer who did not carry mutations, non-Jewish control patients with breast cancer, and healthy Jewish control subjects. Risks were calculated separately for subgroups of probands diagnosed under the age of 50 years and for probands with BRCA1 or BRCA2 gene mutations. RRs were estimated by use of the Cox proportional hazards model. The risks of male breast cancer and of cancer at other sites were calculated in a similar manner. Because there was such a large number of families and the average family size was small, the assumption of no within-family association was considered to be valid.

Penetrance estimates were constructed from the cumulative risks by use of the kin–cohort method described by Wacholder et al. *(12)*. In this method, one half of the first-degree relatives of carriers are assumed also to be carriers. Another assumption is that relatives of probands may carry other BRCA1 and BRCA2 gene mutations at the frequency at which they occur in the Jewish population.

We also evaluated the importance of nonhereditary risk factors for breast cancer in the Jewish population. An analysis that included all case patients and control subjects showed a statistically significantly later age at first birth and greater oral contraceptive use in the control subjects (data available from the authors upon request). However, because we found strong temporal trends for these variables (inversely related to age of the subject) and because the control subjects were younger than the case patients, an age-matched design was thought to be more appropriate despite the limitation of only being able to use a subset of the data. To do this analysis of nonhereditary risk factors, a set of 221 pairs of age-matched Jewish case patients and Jewish control subjects was generated. Each case patient was matched with a single control subject, born within 1 year of the case patient. Reproductive and other risk factors were compared for case patients and control subjects. The statistical significance of the differences in proportions was assessed with McNemar's test, and the differences in means were assessed with the Wilcoxon paired-sign test. The reproductive and cigarette smoking histories for case patients and control subjects were considered only for the period before the age at cancer diagnosis in the case patient. To evaluate the possibility of interactions between mutation status and nongenetic risk factors, we compared the subgroups of case patients who were mutation carriers or noncarriers with their matched control subjects.

RESULTS

Mutation Frequency

From November 1, 1996, through May 31, 1998, 700 eligible Jewish patients with breast cancer were identified and approached. Of these, 457 (65.3%) case patients agreed to participate (Toronto-Sunnybrook Regional Cancer Centre, 128 patients; Sir Mortimer B. Davis-Jewish General Hospital, 112 patients; Mount Sinai Hospital, 85 patients; The Toronto Hospital, 48 patients; Women's College Hospital, 45 patients; and North York General Hospital, 39 patients). Also enrolled were 360 non-Jewish control patients with breast cancer and 380 healthy Jewish women, who served as control subjects. Characteristics of the study subjects were as follows: The mean current age was 61.1 years (95% CI = 60.0–62.1) for the 457 Jewish case patients, 59.1 years (95% CI = 58.1–60.2) for the 360 non-Jewish control patients, and 52.6 years (95% CI = 51.4–53.7) for the 380 Jewish control subjects. The mean age at diagnosis was 54.3 (95% CI = 53.3–55.4) for the case patients and 53.2 years (95% CI = 52.0–54.3) for the non-Jewish control patients. The mean time since diagnosis was 6.7 years (95% CI = 6.2–7.3) for the case patients and 6.0 years (95% CI = 5.5–6.5) for the control patients. The mean total number of first-degree relatives was 5.9 (95% CI = 5.7–6.1) for the case patients, 6.4 (95% CI = 6.1–6.7) for the control patients, and 5.7 (95% CI = 5.5–5.9) for the control subjects. The mean current age of all first-degree relatives was 53.9 years (95% CI = 53.1–54.8) for the case patients, 54.3 years (95% CI = 53.5–55.2) for the control patients, and 48.3 years (95% CI = 47.3–49.3) for the control subjects.

Of the 412 Jewish case patients with breast cancer who underwent mutation analysis, 48 (11.7%) carried one of the three founder mutations: 26 case patients (6.3%) carried 185delAG, eight (1.9%) carried 5382insC, and 15 (3.6%) carried 6174delT. One case patient carried both the 185delAG and the 6174delT mutations. The mean age at diagnosis of the case patients carrying a mutation was statistically significantly younger than that of the case patients who were noncarriers (45.1 years versus 55.3 years; two-sided $P<.001$; Wilcoxon test). The age at diagnosis was 2 years older for BRCA2 gene mutation carriers (46.4 years) than for BRCA1 gene mutation carriers (44.4 years), but this difference was not statistically significant (two-sided $P = .36$; Wilcoxon test). For carriers diagnosed before age 40 years, 85% of mutations were in BRCA1; at the age of 50 years and older, the distribution of BRCA1 and BRCA2 mutations was more even (Table 1, A).

The likelihood of carrying a mutation was strongly related to both age at onset of breast cancer (Table 1, A) and family history of breast and ovarian cancers (Table 1, B). Among the 164 case patients diagnosed before the age of 50 years, 22% were mutation carriers. The highest frequency of mutations (44.4%) was seen in the group of case patients diagnosed between ages 30 and 40 years. In contrast, the mutation frequency in case patients diagnosed at the age of 60 years and older was only 2.2%. Among the 273 case patients with a negative family history (no first-, second-, or third-degree relative diagnosed with breast cancer before age 50 years or ovarian cancer at any age), the mutation carrier frequency was 5.5%: 33.3% for case patients diagnosed before age 40 years, 9.3% for case patients diagnosed at age 40–49 years, 1.3% for case patients diagnosed at age 50–59 years, and 1.0% for case patients diagnosed at age 60 years or older. Among case patients with a positive family history, the mutation frequency was higher (23.7%): 54.5% for case patients diagnosed before age 40 years, 27.6% for case patients diagnosed at age 40–49 years, 25.8% for case patients diagnosed at age 50–59 years, and 5.7% for case patients diagnosed at age 60 years or older. Among the families with mutations, there were six families in which only first cousins were affected. This finding suggests that third-degree relatives may contribute valuable information to an individual's family history of disease. A family history of ovarian cancer was a particularly strong predictor of the presence of a mutation (odds ratio = 7.1; two-sided $P<.001$; Fisher's exact test). Forty-six of 48 mutations occurred in case patients with early-onset breast cancer (<50 years) or a history of ovarian or early-onset breast cancer in a first-, second-, or third-degree relative.

Risk of Cancer for First-Degree Relatives

A total of 130 cases of breast cancer were reported among the 1367 first-degree female relatives of Jewish case patients. The cumulative incidence of breast

Table 1. Frequency of gene mutations

A) By age of Jewish case patients				
Age group	Total*	BRCA1 mutation, No. (%)	BRCA2 mutation, No. (%)	Either mutation, No. (%)
20–29 y	3	1 (33.0)	0 (0.0)	1 (33.0)
30–39 y	27	10 (37.0)	2 (7.4)	12 (44.4)
40–49 y	134	16 (11.9)	8 (6.0)	23 (17.2)
50–59 y	111	5 (4.5)	4 (3.6)	9 (8.1)
⩾60 y	137	2 (1.5)	1 (0.7)	3 (2.2)
Total	412	34 (8.3)	15 (3.6)	48 (11.7)
Two-sided *P* for trend		<.001	.018	<.001
B) By family history of breast and ovarian cancers				
No. of relatives <50 y old who have breast cancer†	Total*,‡	BRCA1 mutation, No. (%)	BRCA2 mutation, No. (%)	Either mutation No. (%)
Breast cancer (no ovarian cancer)				
0	273	11 (4.0)	4 (1.5)	15 (5.5)
1	72	8 (11.1)	4 (5.6)	12 (16.7)
⩾2	25	4 (16.0)	2 (8.0)	5 (20.0)
Breast–ovarian cancers§				
0	23	3 (13.0)	1 (4.3)	4 (17.4)
1	11	5 (45.5)	3 (27.3)	8 (72.7)
⩾2	4	2 (50.0)	1 (25.0)	3 (75.0)

*The woman who carried a BRCA1 gene mutation and a BRCA2 gene mutation is included in both columns.

†Number of first-, second-, or third-degree relatives, excluding case patient.

‡Four subjects were excluded because their family history of ovarian cancer was not confirmed.

§At least one case of ovarian cancer in the case patient or in a first-, second- or third-degree relative.

cancer among the first-degree female relatives of the Jewish case patients was statistically significantly greater than that among the relatives of the non-Jewish control patients (Table 2, A) or the Jewish control subjects (Table 2, B). The RR for breast cancer to age 85 years, given an affected first-degree Jewish relative, based on the Cox proportional model was 1.78 (95% CI = 1.28–2.48) compared with relatives of healthy Jewish control subjects, and the RR was higher when the breast cancer in the index case patient occurred before age 50 years (RR = 2.69; 95% CI = 1.82–3.97) (Fig. 1, A). The risk was increased for relatives of mutation carriers (RR = 5.16; 95% CI = 3.14–8.48) and for relatives of noncarriers (RR = 1.66; 95% CI = 1.18–2.33) (Fig. 1, B). The estimated penetrance to age 70 years for breast cancer was 59.9% for the BRCA1 gene mutations and 28.3% for the BRCA2 gene mutation. Because there were only two ovarian cancers reported in the first-degree relatives of the mutation carriers, penetrance could not be estimated with accuracy.

The risks of all types of cancer in first-degree relatives of case patients and control patients are compared in Table 2, A. There were statistically significantly more cases of lung cancer in the relatives of the non-Jewish control patients than in relatives of the Jewish case patients. The risk of prostate cancer was statistically significantly higher in the first-degree relatives of Jewish case patients with breast cancer than in first-degree relatives of Jewish control subjects (RR = 3.36; 95% CI = 1.49–7.56; Table 2, B). The risk was even higher for the relatives of BRCA1 or BRCA2 gene mutation carriers (Table 2, C). The estimated cumulative risk for prostate cancer in BRCA1 carriers was 33% to age 85 years (five cancers in 93 relatives) and 26% in BRCA2 mutation carriers (two cancers in 34 relatives). One case of male breast cancer was observed in a first-degree relative of a BRCA1 mutation carrier, and one case was seen in a first-degree relative of a BRCA2 mutation carrier. There was one case of early-onset pancreatic cancer in a first-degree relative of a BRCA1 mutation carrier as well as an excess of head and neck cancer (three cases) in first-degree relatives of BRCA2 mutation carriers.

Because the case patients were, on average, 8.5 years older than the control subjects and because there are strong temporal trends in oral contraceptive use and

Table 2. Cumulative incidence of cancer (CIC)

A) In first-degree relatives of Jewish case patients with breast cancer and non-Jewish control patients with breast cancer*

	CIC, %, to age 60 y†			CIC, %, to age 85 y†		
Site	Non-Jewish	Jewish	*P*‡	Non-Jewish	Jewish	*P*‡
Breast, female	6.2	8.7	.024	17.1	25.1	.024
Breast, male	0.0	0.2	.175	0.0	1.0	.044
Ovary	0.4	0.8	.413	0.7	2.5	.103
Prostate	0.7	0.0	.035	11.2	14.8	.842
Colon	0.6	1.0	.301	5.5	7.2	.263
Pancreas	0.1	0.1	.613	0.6	1.8	.188
Lung	1.0	0.6	.178	7.3	4.3	.014
Head and neck	0.5	0.4	.635	2.0	1.2	.198
PSU§	0.5	0.4	.860	2.2	2.9	.643
Any female (except breast)‖	7.7	7.1	.532	25.4	29.6	.663
Female	13.4	15.2	.257	38.8	48.7	.061
Male	7.8	7.1	.963	43.9	46.1	.847
All	10.6	11.3	.316	40.8	47.4	.173

B) In first-degree relatives of Jewish case patients with breast cancer and Jewish control subjects¶

	CIC, %, to age 60 y†			CIC, %, to age 85 y†		
Site	Control	Case	*P*‡	Control	Case	*P*‡
Breast, female	4.8	8.7	.003	11.6	25.1	<.001
Breast, male	0.0	0.2	.237	0.0	1.0	.066
Ovary	0.9	0.8	.776	1.4	2.5	.718
Prostate	0.0	0.0	—	3.6	14.8	.002
Colon	0.7	1.0	.462	6.4	7.2	.946
Pancreas	0.0	0.1	.234	2.9	1.8	.630
Lung	0.2	0.6	.172	4.7	4.3	.763
Head and neck	0.2	0.4	.350	0.5	1.2	.361
PSU§	0.0	0.3	.039	2.2	2.9	.536
Any female (except breast)‖	5.0	7.1	.126	27.1	29.6	.285
Female	9.4	15.2	.001	35.7	48.7	.001
Male	4.2	7.1	.055	36.1	46.1	.013
All	6.9	11.3	<.001	35.6	47.4	<.001

C) In first-degree relatives of Jewish case patients with breast cancer: mutation carriers versus non-carriers#

	CIC, %, to age 60 y†			CIC, %, to age 85 y†		
Site	Noncarrier	Carrier	*P*‡	Noncarrier	Carrier	*P*‡
Breast, female	7.6	27.1	<.001	25.3	44.2	<.001
Breast, male	0.2	1.0	.059	0.8	3.4	.020
Ovary	0.7	3.2	.019	1.9	12.0	.019
Prostate	0.0	0.0	—	12.6	33.6	.049
Colon	0.9	1.2	.960	6.8	11.8	.339
Pancreas	0.1	0.9	.041	1.4	3.3	.127
Lung	0.7	0.0	.425	4.7	2.9	.835
Head and neck	0.2	1.9	<.001	1.3	1.9	.014
PSU§	0.2	1.9	.001	3.0	1.9	.166
Any female (except breast)‖	5.9	18.6	<.001	28.0	47.0	.001
Female	13.2	40.6	<.001	47.9	70.4	<.001
Male	7.3	6.6	.547	45.3	50.9	.029
All	10.4	23.5	<.001	46.7	61.3	<.001

*For female cancers, there were 1154 non-Jewish female relatives of control patients and 1367 Jewish female relatives of case patients. For male cancers, there were 1161 non-Jewish male relatives of control patients and 1316 Jewish male relatives of case patients.

†Kaplan–Meier estimates.

‡Logrank test. All *P* values are two-sided.

§PSU = primary site unknown.

‖Female relatives with breast cancer are considered to be at risk for other cancers.

¶For female cancers, there were 1109 female relatives of control subjects and 1367 female relatives of case patients. For male cancers, there were 1065 male relatives of control subjects and 1316 male relatives of case patients.

#For female cancers, there were 1112 female relatives of noncarriers and 128 female relatives of carriers. For male cancers, there were 1046 male relatives of noncarriers and 129 male relatives of carriers.

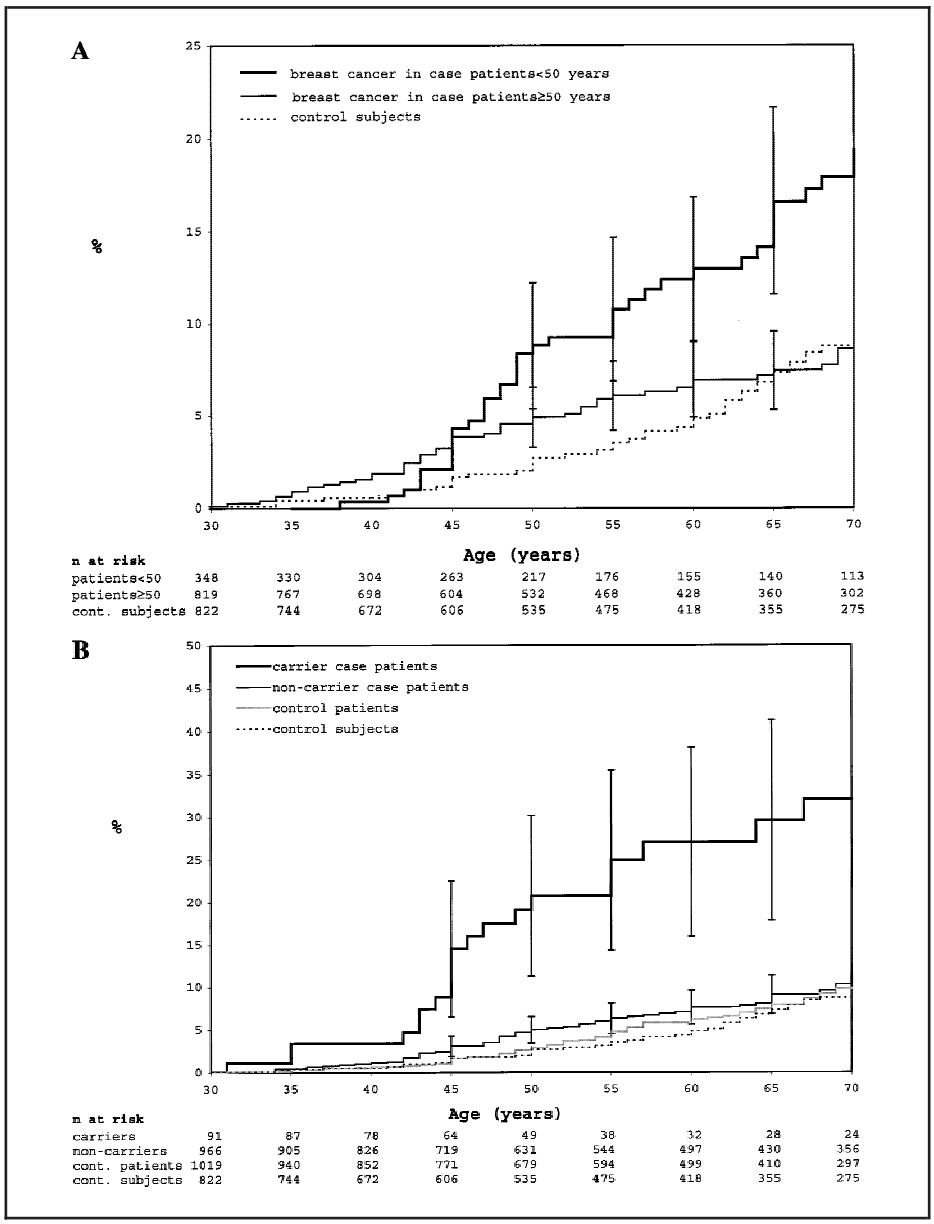

Fig. 1. A) Cumulative incidence of breast cancer in female first-degree relatives of Jewish study subjects. We observed 41 cases of breast cancer among the 492 female relatives of case patients whose breast cancer was diagnosed before the age of 50 years, 51 cases of breast cancer among the 875 female relatives of case patients whose breast cancer was diagnosed at or after the age of 50 years, and 45 cases of breast cancer among the 1109 female relatives of the healthy Jewish control subjects. **B**) Cumulative incidence of breast cancer in female first-degree relatives of study subjects. We observed 20 cases of breast cancer among the 128 female relatives of Jewish case patients with a BRCA1 or a BRCA2 gene mutation, 69 cases of breast cancer among the 1112 female relatives of Jewish case patients who did not carry a mutation, 64 cases of breast cancer among the 1154 female relatives of non-Jewish control patients, and 45 cases of breast cancer among the 1109 female relatives of healthy Jewish control subjects.

parity with year of birth, an age-matched analysis was performed to evaluate the effect of nonhereditary risk factors (Table 3). No statistically significant differences were found for any of the nonhereditary risk factors between Jewish case patients and Jewish control subjects. In a subgroup analysis, BRCA1/BRCA2 mutation carriers had used oral contraceptives more often than noncarriers (72.7% versus 56.2%), but this difference was not statistically significant after adjustment was made for the age difference.

Discussion

In our population of 412 Ashkenazi Jewish case patients with breast cancer in Toronto and Montreal, who were unselected for age or a family history of breast cancer, the overall mutation carrier frequency was 11.7%. The likelihood of finding a mutation was highly dependent on the age of the patient and her family history of breast and ovarian cancers. The mutation frequency was very high in case patients diagnosed before the age of 40 years (43.3%). In contrast, the rate of mutations among case patients diagnosed at the age of 60 years or older was 2.2% and was not higher than that expected from population studies *(4).* For case patients diagnosed at the age of 50 years or older who lacked a family history of breast or ovarian cancer, the mutation frequency was even lower. Because almost 300 000 of the 350 000 Jews in Canada live in the greater Toronto and Montreal areas and because the majority of Jewish women with breast cancer in Toronto and Montreal are treated in one of these six hospitals, we believe that our results can be generalized to the Jewish population in Canada.

There are two smaller reports *(13,14)* of the mutation frequency in Jewish women with breast cancer, who were unselected for age or a family history of breast cancer. Fodor et al. *(13)* tested a consecutive series of 268 patients with incident cases of breast cancer who had a median age at diagnosis of 59 years. They found a mutation carrier frequency of only 6.8% overall and of 16% for women diagnosed before age 42 years. Abeliovich et al. *(14)* tested 162 patients with breast cancer in Israel who had a median age at diagnosis of less than 50 years. They found a mutation carrier frequency of 13.5% overall and of 30% for women diagnosed before age 40 years. Criteria for defining patients as Jewish in either study were not given; however, marriages between Jews and non-Jews are uncommon in Israel. Differences in geographic origin of the patients might also account for variation in carrier frequencies.

Other studies *(10,15,16)* that have focused on women with premenopausal or familial cases of breast cancer have found carrier frequencies similar to ours. Our finding that 40% of the case patients who had a family history of ovarian cancer carried mutations is similar to the report of Tonin et al. *(17).*

Our estimated penetrance of breast cancer to age 70 years of 59.9% for BRCA1 gene mutations is similar to the estimate of Struewing et al. *(7),* which was based on an unselected group of Jewish volunteers and which was lower than penetrance estimates derived from high-risk families *(18,19).* Struewing et al. es-

Table 3. Comparison of nongenetic risk factors in Jewish case patients with breast cancer and Jewish control subjects*

Characteristic	Jewish case patients (n = 221)	Jewish control subjects (n = 221)	Two-sided *P*
Year of birth, mean (95% CI)	41.6 (40.2–43.0)	41.7 (40.3–43.1)	—
Current age, y, mean (95% CI)	55.9 (54.5–57.4)	55.5 (54.1–56.9)	—
Reproductive history, mean (95% CI)			
Age at menarche, y	12.5 (12.4–12.7)	12.5 (12.3–12.8)	.652
Parity	2.1 (1.9–2.2)	2.1 (1.9–2.2)	.897
Age at first live birth, y	25.9 (25.2–26.5)	25.8 (25.2–26.5)	.867
Age at last live birth, y	30.7 (30.1–31.4)	30.5 (29.8–31.2)	.567
Oral contraceptive use			
Ever users, %	57.9	61.1	.581
Duration, y, mean (95% CI)	3.4 (2.8–4.1)	2.9 (2.4–3.5)	.703
Height, cm, mean (95% CI)	161.3 (160.3–162.3)	161.5 (160.7–162.3)	.888
Weight, kg,† mean (95% CI)	66.9 (65.2–68.6)	66.4 (64.6–68.1)	.330
BMI,† mean (95% CI)	25.9 (25.1–26.5)	25.3 (24.8–26.0)	.115
Ever smoked, %	53.8	48.9	.347
Pack-years,‡ mean (95% CI)	7.2 (5.5–9.0)	7.0 (5.0–9.1)	.557

*For the continuous variables, we have used the Wilcoxon paired sign test. For dichotomous exposure, we have used McNemar's test. CI = confidence interval.

†Two Jewish case patients and one Jewish control subject had missing weight and body mass index (BMI) information.

‡Pack-years = number of cigarette packs smoked per day × number of years of smoking.

timated the penetrance of the BRCA2 mutation to be only slightly lower than that of the BRCA1 mutation, but we estimated the penetrance to age 70 years of BRCA2 to be 28.3%. Although our estimate must be interpreted with caution because it is based on a small number of cases, it is similar to the estimate of 37.2% to age 70 years from a population-based study in Iceland *(20)*. Furthermore, our observed frequency of BRCA2 mutations was much lower than the frequency of BRCA1 mutations (3.6% versus 8.3%), despite the fact that these mutations are almost equally numerous in the Jewish population *(4–7)*. These data are consistent with the conclusions of others that the penetrance of BRCA2 is lower than that of BRCA1 *(5,6)*.

The average time from diagnosis to interview among the Jewish case patients was 6.7 years. If there are survival differences between carriers and noncarriers, then our population may not be representative and our mutation frequency may be biased. At present, the literature in this regard is in conflict *(21–25)*, and we await results of prospective studies. In our study, there was no clear difference in mutation frequency between recently diagnosed case patients and long-term survivors; among case patients with 5 years or more of follow-up, the frequency was 11.8% compared with 11.6% for those followed for less than 5 years. The patients who declined mutation testing were slightly older than those who accepted testing (63.1 years and 60.8 years, respectively). This difference might elevate our overall mutation frequency but should not affect our age-specific mutation frequencies. Review of medical records at Toronto-Sunnybrook Regional Cancer Centre, the institution that contributed the largest number of case patients, revealed no difference in the age at onset of breast cancer or family history of breast or ovarian cancer of Jewish patients who had died compared with Jewish case patients who had undergone genetic testing.

We found the risk of breast cancer in the first-degree relatives of the Jewish case patients who were not mutation carriers to be statistically significantly greater than the risk for the relatives of the healthy Jewish control subjects. This observation supports the conclusion of Claus et al. *(26)*, who suggested that there are genetic factors beyond the three founding mutations that contribute to the heritability of breast cancer in the Jewish population. It is not known whether this excess risk is due to additional mutations in BRCA1 or BRCA2 or to mutations in other susceptibility genes. Common lifestyle or environmental factors might also explain part of the familial clustering.

We found a statistically significantly greater risk of prostate cancer after age 60 years in the first-degree male relatives of the Jewish case patients than in the first-degree male relatives of the Jewish control subjects. The risks were somewhat greater when the proband carried a BRCA1 or BRCA2 gene mutation. A moderately increased risk of prostate cancer in mutation carriers has been described *(7,27–29);* however, other investigators *(30–32)* did not find a higher than expected number of mutation carriers among Jewish men with prostate cancer. Because, for prostate cancer, the youngest age of onset reported in a carrier family in our study was 69 years, we do not advocate screening male carriers for prostate cancer before age 50 years *(33)*.

Statistically significantly elevated risks in relatives of carriers were also found for head and neck cancer and for pancreatic cancer. Although these findings must be interpreted with caution, given the multiple comparisons that we have made, they are consistent with the results of other investigators *(7,11,34,35)*.

We studied 2683 relatives of the 457 case patients, 2315 relatives of 360 control patients, and 2174 relatives of 380 control subjects. Because we included multiple relatives for each case and control group, the independence assumption can be questioned. However, the number of families was very large compared with the average number of relatives per family, which should minimize this effect. Nonetheless, we also repeated our analyses using only data derived from the 2302 parents (who are not known to be related). The results are essentially the same as those presented in Table 2 (data available from the authors upon request).

Our findings have important implications for genetic screening of Jewish patients with breast cancer and for counseling their relatives. These data support the position that testing should be offered to all Jewish women with breast cancer diagnosed before the age of 50 years or who have a first-, second-, or third-degree relative with ovarian or early-onset breast cancer. Using these criteria, we would have identified 46 of the 48 mutations present in this dataset by screening 231 of 412 case patients.

We estimate that approximately 12% of the cases of breast cancer in the Jewish population are attributable to the three founding mutations, including 22% of cancers diagnosed before age 50 years. This percentage compares with an estimate of 3% for BRCA1 mutations in non-Jewish women with breast cancer *(36)*

and a similar prevalence for the BRCA2 mutation *(37)*. In our study, genetic risk factors were of greater importance than the nongenetic risk factors. We did not find that reproductive histories differed statistically significantly between the Jewish case patients and control subjects. These data support the hypothesis that the excess risk of breast cancer observed in the Jewish population is largely attributable to genetic factors.

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NOTES

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