

# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JULY 12, 2007

VOL. 357 NO. 2

## Clinical Outcomes of Breast Cancer in Carriers of *BRCA1* and *BRCA2* Mutations

Gad Rennert, M.D., Ph.D., Shantih Bisland-Naggan, M.P.H., Ofra Barnett-Griness, Ph.D., Naomi Bar-Joseph, M.A., Shiyu Zhang, M.D., Hedy S. Rennert, M.P.H., and Steven A. Narod, M.D.

### ABSTRACT

#### BACKGROUND

Some features of breast cancer in women with a *BRCA1* mutation suggest that hereditary breast cancer has a poor outcome. We conducted a national population-based study of Israeli women to determine the influence, if any, of a *BRCA1* or a *BRCA2* mutation on the prognosis in breast cancer.

#### METHODS

We obtained data on all incident cases of invasive breast cancer that were diagnosed from January 1, 1987, to December 31, 1988, and recorded in the Israel National Cancer Registry. We requested a paraffin-embedded tumor block or an unstained slide and the corresponding pathological and clinical records for all such cases. DNA extracted from the tumor specimens was analyzed for the three founder mutations in *BRCA1* and *BRCA2*. For each subject, available pathological and oncologic records were reviewed.

#### RESULTS

We were able to retrieve a pathological sample from 1794 of 2514 subjects (71%). Among those women, we obtained medical records for 1545 (86%). A *BRCA1* or *BRCA2* mutation was identified in 10% of the women who were of Ashkenazi Jewish ancestry. The adjusted hazard ratios for death from breast cancer were not significantly different among mutation carriers and noncarriers (hazard ratio among *BRCA1* carriers, 0.76; 95% confidence interval [CI], 0.45 to 1.30;  $P=0.31$ ; hazard ratio among *BRCA2* carriers, 1.31; 95% CI, 0.80 to 2.15;  $P=0.28$ ). Among women who were treated with chemotherapy, the hazard ratio for death among *BRCA1* carriers was 0.48 (95% CI, 0.19 to 1.21;  $P=0.12$ ).

#### CONCLUSIONS

Breast cancer-specific rates of death among Israeli women are similar for carriers of a *BRCA* founder mutation and noncarriers.

From Clalit Health Services, National Cancer Control Center and Department of Community Medicine and Epidemiology, Carmel Medical Center and B. Rappaport Faculty of Medicine, Technion, Haifa, Israel (G.R., S.B.-N., O.B.-G., N.B.-J., H.S.R.); and the Women's College Research Institute, University of Toronto, Toronto (S.Z., S.A.N.). Address reprint requests to Dr. Rennert at the Clalit Health Services, National Cancer Control Center, Carmel Medical Center, Haifa 34362, Israel, or at [rennert@tx.technion.ac.il](mailto:rennert@tx.technion.ac.il).

N Engl J Med 2007;357:115-23.

Copyright © 2007 Massachusetts Medical Society.

**B**REAST CANCER IS THE LEADING CAUSE of all deaths from cancer among Israeli women.<sup>1</sup> Approximately 3800 women receive the diagnosis of breast cancer annually in this population; in 28% of these women, breast cancer is diagnosed before the age of 50 years.<sup>1</sup> To some extent, the high proportion of cases in young women reflects the high prevalence of hereditary breast cancers in Jewish women.

Approximately 60% of Israeli Jews are Ashkenazi, and others are Sephardi, Iraqi, or of mixed ancestry; there are also Muslim, Christian, and Druze residents. Two mutations in *BRCA1* (185delAG and 5382insC) and one in *BRCA2* (6174delT) are common in Ashkenazi women. Approximately 2% of all Ashkenazi women<sup>2,3</sup> and 12% of Ashkenazi women with breast cancer<sup>4</sup> carry a mutation in one of these two genes. Much of the information that correlates mutational status with breast-cancer type has come from studies of the Ashkenazi population, but little is known about the influence of a *BRCA1* or *BRCA2* mutation on the natural history of breast cancer or the response to treatment. *BRCA1*-associated breast cancers often occur in younger women, and such tumors are high grade and lack estrogen receptors.<sup>5,6</sup> All these features are associated with a poor prognosis. However, the evidence concerning the effect of a *BRCA1* or *BRCA2* mutation on the prognosis is inconsistent.<sup>7-14</sup> To clarify the influence of these mutations on the outcome in breast cancer, we evaluated 10-year survival rates in a national cohort of Israeli women whose breast cancer had been diagnosed in 1987 or 1988.

---

## METHODS

---

### STUDY PATIENTS

We identified women who had received the diagnosis of invasive breast cancer in Israel between January 1, 1987, and December 31, 1988, through the records of the Israel National Cancer Registry. This registry records the woman's name, birth date, and national identification number and information on the treating hospital and selected tumor characteristics (morphologic type and stage). It records information for more than 95% of women with breast tumors diagnosed in Israel.<sup>15</sup> Women identified through the registry were linked to the Israel Population Register to ascertain their probable ethnic origin. Information in the register includes whether the woman is Jewish, the

country of birth for women born abroad, and the places of birth of both parents for women born in Israel. Probable ethnic group was assigned for each woman with breast cancer. Jewish women born in Europe, North America, South America, and South Africa were defined as Ashkenazi unless a different ethnic background was stated in the medical records. Jews born in Asia (mostly in the Arab countries of the Middle East, Iran, and India) and North Africa were considered to be Sephardi. Iraqi Jews were assigned their own category. Jews born in Israel were classified according to the country of birth of their parents, when data were available. If parental origin was not available or if the parents had different ethnic backgrounds, the ancestry was assigned as Ashkenazi.

For each eligible subject, we requested one or more paraffin-embedded tumor blocks or unstained slides and the corresponding pathological and oncologic records from the treating hospital. The records were reviewed for pathological stage (including the size of the tumor and the number of lymph nodes that were evaluated and were malignant), histological analysis of the tumor, and estrogen-receptor status. Information on grade was not routinely recorded during the study years, and estrogen-receptor data were available for only 55% of subjects. We extracted information from the medical records for clinical stage, treatment, and outcome. The main outcomes of interest were overall survival and death from breast cancer. Other outcomes, such as local recurrence, contralateral breast cancer, and other primary cancers, were also recorded (see the table in the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)). The stage at diagnosis was assigned to each subject on the basis of all the information available to the investigators from the pathological reports and the clinical-oncology records. We extracted data on the cause of death from the official records of the Central Bureau of Statistics of Israel, which was coded on the basis of nomenclature from the *International Classification of Diseases, 9th Revision*.

The study was approved by the institutional review board at Carmel Medical Center in Haifa, Israel, and by the Israeli Ministry of Health. These investigations were conducted according to guidelines for the protection of human subjects issued by the Carmel Medical Center, the Israel National Cancer Registry, the National Cancer Insti-

tute in Bethesda, Maryland, and the University of Toronto.

We identified 2729 subjects with invasive breast cancer who were treated at 24 hospitals. Two hospitals had discarded their tumor samples before the study began, and the 215 subjects at these hospitals were therefore excluded. Among the remaining 2514 subjects, we retrieved a pathological sample from 1794 (71%). DNA was extracted from the paraffin blocks and was analyzed for the three founder mutations in the *BRCA1* and *BRCA2* genes. We used a method described previously<sup>16</sup> to assign mutational status to all 1794 women for whom samples were available. We were able to retrieve medical records for 1545 of these women (86%).

#### STATISTICAL ANALYSIS

The prevalence of *BRCA1* and *BRCA2* mutations was determined for each ethnic subgroup as the proportion of mutation-positive subjects among all subjects. We compared demographic and clinical features between *BRCA* carriers and noncarriers with the use of the chi-square test, Fisher's exact test, Mann-Whitney test, or t-test, as appropriate. All women in the study were followed for 16 years for survival and incidence of other cancers. Information on cause of death was available for deaths that occurred during the first 10 years of follow-up. The 10-year overall survival rates were calculated as the number of women who were alive after 10 years divided by the number of women in the cohort. These proportions were compared between groups with the use of either the chi-square test or Fisher's exact test. Both the time to death and the time to death from a breast-cancer-specific cause were compared with the use of Kaplan-Meier curves, and statistical significance was evaluated with the use of the log-rank test. The Cox proportional-hazards model was used to estimate the hazard ratio for carriers of the mutation, as compared with noncarriers, after adjustment for age, tumor size, lymph-node status, and metastases.

---

## RESULTS

---

#### MUTATION RATES ACCORDING TO ETHNIC GROUP

Tumor samples were obtained from 1794 subjects who had received the diagnosis of breast cancer in Israel in 1987 or 1988. All but 46 of the subjects were Jewish women. Among these 1748 Jewish

women, 1102 were Ashkenazi, 418 were Sephardi, 87 were Iraqi, and 141 were of other, unknown, or mixed ancestry. Table 1 shows the characteristics of the tumors in the various ethnic subgroups. All tumor samples were tested for the presence of the three founder mutations. No mutation was detected in any of the 46 women who were not Jewish. A mutation was detected in 135 samples from 1748 Jewish women (8%); these included 105 of 1102 samples from Ashkenazi women (10%), 6 of 87 from Iraqi women (7%), and 4 of 418 from Sephardic women (1%). The ethnic origin of an additional 20 of 131 Jewish carriers of the mutations (15%) who were born in Israel could not be assigned (and were listed as unclassified). For 10 Jewish subjects, there was no information on either country of birth or ethnic group.

After the 218 Iraqi and unclassified women had been reassigned to the group with the Ashkenazi women, the prevalence of mutation carriers in this newly defined Ashkenazi group with breast cancer was 10%.

In the newly defined Ashkenazi group, 131 women were carriers; 76 had *BRCA1* mutations, 52 had *BRCA2* mutations, and 3 had mutations in both genes and thus were excluded from all analyses. Among the 336 Ashkenazi women whose breast cancer had been diagnosed before the age of 50 years, the prevalence of the mutation was 18%; among the 984 women who were 50 years of age or older when they received the diagnosis, the prevalence was 7%.

#### CHARACTERISTICS OF BREAST CANCERS

We used pathological reports from all participating pathology institutes to compare the tumors in the 131 Ashkenazi women who had a mutation with the tumors in the 1189 Ashkenazi women for whom no mutation was identified (Table 2). The mean age at diagnosis was lower in *BRCA1* carriers than in noncarriers (52 vs. 61 years,  $P<0.001$ ). In contrast to the other two groups, most of the *BRCA1* carriers received the diagnosis of breast cancer before the age of 50 years. Tumor size and lymph-node status were similar in the three groups. *BRCA1* carriers were less likely to have estrogen-receptor-positive tumors than were noncarriers (24% vs. 65%,  $P<0.001$ ). The difference between carriers and noncarriers was marked for tumors that were reported to be strongly estrogen-receptor-positive (0% of *BRCA1* carriers vs. 31% of noncarriers,  $P<0.001$ ).

**Table 1. Characteristics of Jewish and Non-Jewish Women with Breast Cancer.\***

Variable	Ashkenazi Jews	Iraqi Jews	Sephardi Jews	Other Jews†	All Jews‡	Non-Jews
No. of subjects	1102	87	418	131	1748	46
Age at diagnosis						
Mean — yr	62.1±13.5	56.2±11.0	54.7±13.2	46.9±11.7	58.8±14.0	49.7±9.9
<50 yr — %	20	26	37	67	29	46
Tumor size						
Median (interquartile range) — cm	2.0 (1.5–3.0)	2.5 (1.8–3.0)	2.5 (1.8–3.5)	2.0 (1.5–3.0)	2.0 (1.5–3.0)	3.0 (2.4–5.0)
<2 cm — %	34	29	27	43	33	16
2–5 cm — %	56	60	58	47	56	58
>5 cm — %	10	11	14	9	11	26
Missing data — no.	157	15	88	25	287	8
Nodal status						
Positive — %	47	44	54	56	49	81
Negative — %	53	56	46	44	51	19
Missing data — no.	127	3	37	18	186	4
Stage						
I — %	31	32	26	30	30	7
II — %	46	43	47	50	46	53
III — %	16	20	19	16	17	33
IV — %	6	4	8	3	6	7
Missing data — no.	76	4	17	16	114	1
Estrogen-receptor status						
Strongly positive — %	30	27	18	15	26	25
Mildly positive — %	33	29	34	36	33	25
Negative — %	37	44	48	48	41	50
Missing data — no.	417	25	153	71	669	18
Excluded — no.§	92	10	41	8	152	0
Alive at 10 yr — %	50	53	51	57	51	52
Mutational status						
No mutation — no. (%)	997 (91)	81 (93)	414 (99)	111 (85)	1613 (92)	46 (100)
BRCA1 — no. (%)	55 (5)	6 (7)	2 (<1)	15 (11)	78 (4)	0
BRCA2 — no. (%)	47 (4)	0	1 (<1)	5 (4)	53 (3)	0
Both mutations — no.	3	0	1	0	4	0

\* Plus-minus values are means ±SD. Percentages may not total 100 because of rounding.

† Women in this category were born in Israel but were of unclassified ethnic origin.

‡ This category includes 10 Jewish women with an unknown country of birth and origin.

§ Data were excluded for patients who were treated at one institution for which estrogen-receptor results were determined to be unreliable.

#### OVERALL SURVIVAL

All subjects were followed for a minimum of 10 years. The crude 10-year survival rates were 51% for Jewish women and 52% for non-Jewish women, but there were only 46 women in the latter category (Table 1). Among Jewish women, 10-year sur-

vival rates were similar for Ashkenazi women (50%) and Sephardi women (51%). Among the Ashkenazi subjects, the presence of a *BRCA* mutation did not significantly influence the overall 10-year survival rate: 49% for *BRCA1* carriers, 48% for *BRCA2* carriers, and 51% for noncarriers (Table 3).

Among the mutation carriers, 89% of deaths were due to cancer, as compared with 72% of the deaths among noncarriers ( $P=0.002$ ). The adjusted hazard ratio for death from any cause did not differ significantly between carriers of *BRCA1* mutations and noncarriers (hazard ratio, 1.13; 95% confidence interval [CI], 0.78 to 1.66;  $P=0.52$ ) or between carriers of *BRCA2* mutations and noncarriers (hazard ratio, 1.20; 95% CI, 0.77 to 1.86;  $P=0.42$ ) (Table 3).

#### MORTALITY FROM BREAST CANCER

The rate of survival at 10 years was 67% for *BRCA1* carriers, 56% for *BRCA2* carriers, and 67% for noncarriers ( $P=0.25$  for the comparison between carriers of either mutation and noncarriers by the log-rank test with 2 degrees of freedom). Of 24 deaths from breast cancer among *BRCA1* carriers, 21 (88%) occurred within 5 years after diagnosis, as compared with 17 of 22 such deaths (77%) in *BRCA2* carriers and 244 of 361 (68%) in noncarriers ( $P=0.04$  for the comparison between carriers of either mutation and noncarriers). Among women who died from breast cancer, the median time to death was 46 months for noncarriers, 37 months for *BRCA1* carriers, and 48 months for *BRCA2* carriers. The adjusted hazard ratios for death from breast cancer did not differ significantly for carriers of *BRCA* mutations as compared with noncarriers (hazard ratio for *BRCA1*, 0.76; 95% CI, 0.45 to 1.30;  $P=0.31$ ; hazard ratio for *BRCA2*, 1.31; 95% CI, 0.80 to 2.15;  $P=0.28$ ) (Table 3).

Among women who did not receive chemotherapy after surgery, the 10-year survival rates were 76% for *BRCA1* carriers and 74% for noncarriers (hazard ratio, 0.93; 95% CI, 0.43 to 2.02;  $P=0.86$ ). Among women who received chemotherapy, the 10-year survival rates were 71% for *BRCA1* carriers and 46% for noncarriers (hazard ratio, 0.48; 95% CI, 0.19 to 1.21;  $P=0.12$ ). The interaction between *BRCA1* mutation status and chemotherapy was significant only for overall survival ( $P=0.02$ ). The survival of *BRCA2* carriers was similar to that for noncarriers, with or without chemotherapy (Table 4).

In univariate analysis of the influence of age, tumor stage and size, and lymph-node status on breast-cancer-specific mortality among mutation carriers and noncarriers, the influence of tumor size and of lymph-node status was significant only among noncarriers ( $P<0.001$ , data not shown). The age-adjusted hazard ratio for death from

**Table 2. Characteristics of Ashkenazi Jewish Women with Breast Cancer, According to Genetic Subgroup.\***

Variable	Noncarrier	<i>BRCA1</i>	<i>BRCA2</i>
No. of patients†	1189	76	52
Age at diagnosis			
Mean — yr	60.9±13.8	52.1±14.8	56.7±12.8
<50 yr — no. (%)	277 (23)	40 (53)	17 (33)
Tumor size			
Median (interquartile range) — cm	2.0 (1.5–3.0)	2.5 (2.0–3.0)	2.0 (2.0–2.5)
≤1 cm — no. (%)	121 (12)	4 (6)	4 (9)
1 to ≤2 cm — no. (%)	410 (41)	23 (34)	19 (41)
>2 to ≤3 cm — no. (%)	246 (24)	26 (39)	16 (35)
>3 cm — no. (%)	230 (23)	14 (21)	7 (15)
Missing data — no.	182	9	6
Lymph-node status			
Positive — no. (%)	499 (47)	31 (44)	24 (52)
Negative — no. (%)	553 (53)	40 (56)	22 (48)
Missing data — no.	137	5	6
Stage			
I — no. (%)	352 (32)	21 (29)	8 (16)
II — no. (%)	494 (45)	41 (57)	30 (61)
III — no. (%)	188 (17)	9 (12)	7 (14)
IV — no. (%)	66 (6)	1 (2)	4 (8)
Missing data — no.	89	4	3
Estrogen-receptor status			
Strongly positive — no. (%)	196 (31)	0	4 (13)
Mildly positive — no. (%)	214 (34)	7 (24)	10 (32)
Negative — no. (%)	225 (35)	22 (76)	17 (55)
Missing data — no.	448	46	19
Excluded — no.‡	106	1	2
Alive at 10 yr — no. (%)	605 (51)	37 (49)	25 (48)

\* Plus-minus values are means ±SD. Percentages may not total 100 because of rounding.

† Numbers of mutation carriers exclude three women who had a double mutation.

‡ Data were excluded for patients who were treated at one institution for which estrogen-receptor results were determined to be unreliable.

breast cancer associated with a *BRCA1* mutation among women with tumors of 2 cm or less was 1.78 (95% CI, 0.83 to 3.84;  $P=0.14$ ); among women with tumors larger than 2 cm, it was 0.62 (95% CI, 0.34 to 1.09;  $P=0.10$ ) (Fig. 1). The interaction between tumor size and carrier status was significant for *BRCA1* ( $P=0.04$ ) but not for *BRCA2* ( $P=0.10$ ). Age did not seem to be a predictor of survival in either noncarriers or carriers of the mutations. For women who were under the age



**Table 3. Ten-Year Survival Rates and Hazard Ratios for Death among Ashkenazi Women with Breast Cancer, According to Genetic Subgroup.**

Group	No. of Subjects	Death from Any Cause				Death from Breast Cancer			
		10-Year Survival %	Unadjusted Hazard Ratio (95% CI)	P Value	Adjusted Hazard Ratio (95% CI)*	10-Year Survival %	Unadjusted Hazard Ratio (95% CI)	P Value	Adjusted Hazard Ratio (95% CI)*
Noncarriers	1189	51	1.0	1.0	1.0	67	1.0	1.0	1.0
BRCA1 carriers	76	49	1.09 (0.79–1.51)	0.58	1.13 (0.78–1.66)	67	1.08 (0.72–1.63)	0.71	0.76 (0.45–1.30)
BRCA2 carriers	52	48	1.07 (0.73–1.58)	0.73	1.20 (0.77–1.86)	56	1.42 (0.92–2.19)	0.11	1.31 (0.80–2.15)

\* Hazard ratios were adjusted for age (<50, 50–70, or >70 yr), tumor size (≤2 or >2 cm), lymph-node status (positive or negative), and status with respect to metastasis (yes or no).

of 50 years at diagnosis, the adjusted hazard ratio for death among women with a BRCA1 mutation was 0.56 (95% CI, 0.26 to 1.23; P=0.15). For women who were 50 years of age or older at diagnosis, those with the BRCA1 mutation and non-carriers had similar survival times (adjusted hazard ratio for death among BRCA1 carriers, 1.07; 95% CI, 0.50 to 2.29; P=0.85) (Fig. 1).

**COMPARISON OF STUDY PARTICIPANTS AND NONPARTICIPANTS**

To determine whether the subjects we studied were representative of all Israeli women with breast cancer, we reviewed registry information for the 935 subjects for whom a tumor specimen was not obtained. The mean age at diagnosis for nonparticipants in the study was slightly older than that for participants (60 vs. 59 years, P=0.03). Nonparticipants were more likely than participants to be deceased (69% vs. 60%, P<0.001). Ashkenazi origin was more frequent among participants than among nonparticipants (62% vs. 53%), whereas Israeli-born Jews of uncertain ethnic background were more frequent among nonparticipants than among participants (17% vs. 7%, P<0.001 for comparisons regarding uncertain ethnic background).

**DISCUSSION**

By examining registry information, we identified the majority of women who had received the diagnosis of breast cancer in Israel in 1987 or 1988 and identified all deaths attributable to breast cancer in the 10-year period after diagnosis. The study was designed to estimate survival rates for women with a BRCA1 or BRCA2 mutation, as compared with women without a detected mutation. These estimates are important to women with a BRCA mutation who face a decision between preventive surgery and intensive surveillance.

In our study, the size of the tumor was not a predictor of the probability of death, and lymph-node status was a predictor of borderline significance. Survival rates were similar for women who had a tumor that was 2 cm or less and those with a tumor of more than 2 cm. Of 20 women with a BRCA1 mutation and a node-negative tumor of 2 cm or less, 3 died of breast cancer within 10 years after diagnosis. The influence of a BRCA1 or BRCA2 mutation on the outcome of chemotherapy was not statistically significant.

Among several previous studies of breast-

**Table 4. Ten-Year Survival Rates and Adjusted Hazard Ratios for Death, According to the Use or Nonuse of Chemotherapy and Genetic Subgroup.\***

Group	No. of Subjects	Death from Any Cause			Death from Breast Cancer			P Value for Interaction between BRCA Status and Chemotherapy
		10-Year Survival	Adjusted Hazard Ratio (95% CI)†	P Value	10-Year Survival	Adjusted Hazard Ratio (95% CI)†	P Value	
		%			%			
Noncarriers		51	1.0		67	1.0		
No chemotherapy	757	56	1.0		74	1.0		
Chemotherapy	235	42	1.0		46	1.0		
<i>BRCA1</i> carriers								OS, 0.02; BCS, 0.21
No chemotherapy	42	45	1.59 (1.01–2.50)	0.04	76	0.93 (0.43–2.02)	0.86	
Chemotherapy	25	68	0.56 (0.24–1.29)	0.17	71	0.48 (0.19–1.21)	0.12	
<i>BRCA2</i> carriers								OS, 0.97; BCS, 0.70
No chemotherapy	29	59	1.14 (0.58–2.24)	0.69	67	1.40 (0.61–3.21)	0.43	
Chemotherapy	17	41	1.04 (0.54–2.01)	0.90	47	1.06 (0.52–2.11)	0.87	

\* Chemotherapy drugs used in combination were cyclophosphamide, methotrexate, and fluorouracil; cyclophosphamide, doxorubicin, and fluorouracil; and cyclophosphamide, mitoxantrone, and fluorouracil. Data regarding chemotherapy were not available for all study patients. OS denotes overall survival, and BCS breast-cancer-specific survival.

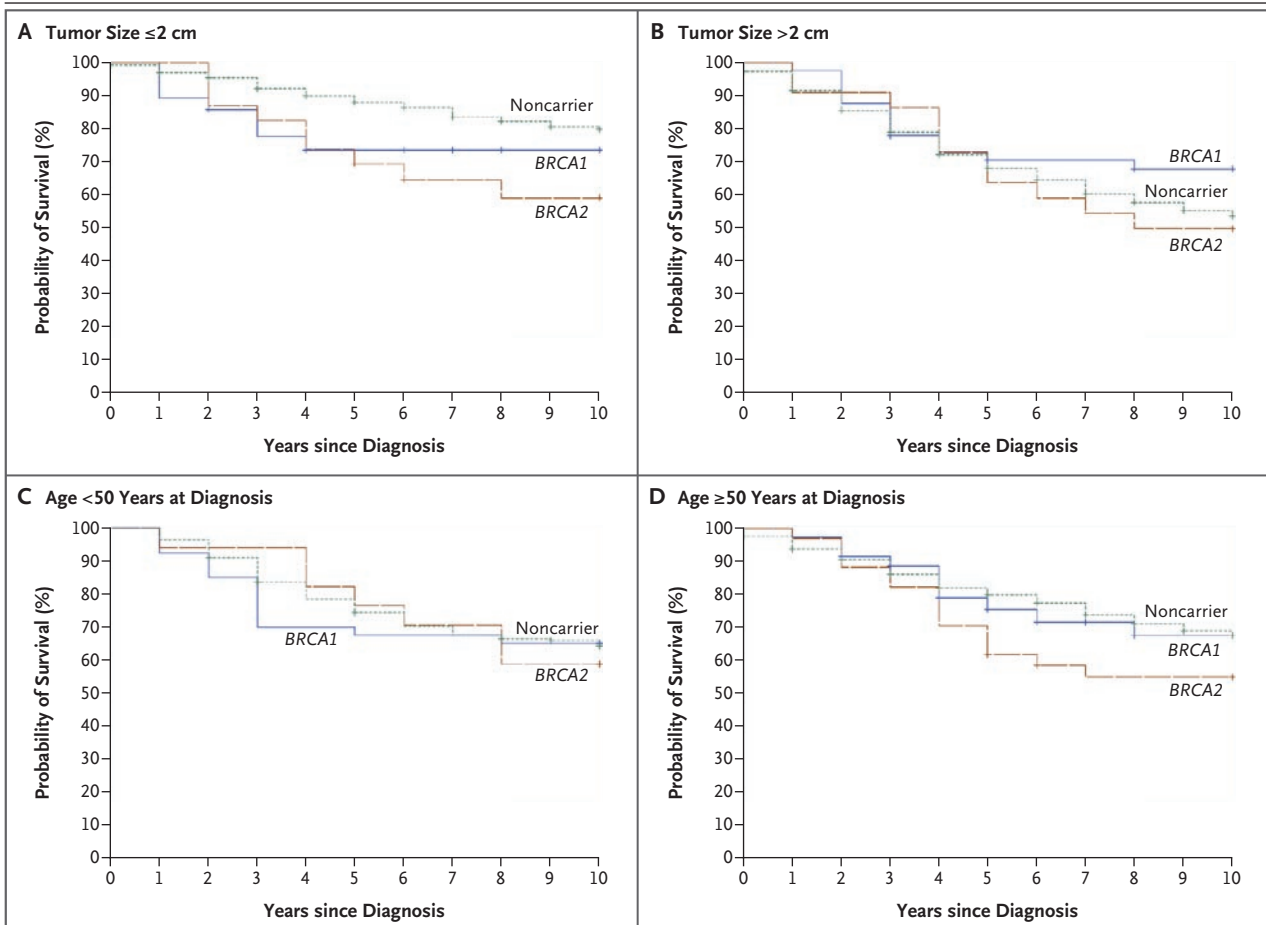
† Data were adjusted for age (<50, 50–70, or >70 yr), tumor size ( $\leq 2$  or  $> 2$  cm), lymph-node status (positive or negative), and status with respect to metastasis (yes or no).

cancer survivorship among *BRCA* carriers, three are notable for robust study designs and relatively large samples. Two of these studies involved Jewish women,<sup>12,13</sup> and the third involved Dutch women.<sup>14</sup> Robson and colleagues<sup>12</sup> used a design similar to ours. They typed tumor blocks from 496 Jewish women with breast cancer who had undergone breast-conserving surgery between 1980 and 1995. Of these women, 56 were found to carry a founder mutation (11%). After a median survival of 10 years, the rate of breast-cancer-specific survival was worse for carriers of *BRCA1* mutations than for noncarriers (62% vs. 86%,  $P < 0.001$ ). This difference was noted regardless of whether women had undergone chemotherapy. Our study is similar to that of Robson et al. except that breast-conserving surgery was not a criterion for selection of our subjects. The 10-year survival rates for the women in our study were lower than those reported by Robson et al.,<sup>12</sup> whose subjects received the diagnosis of breast cancer in New York or Montreal. Less than half of the Israeli women in our study had tumors of 2 cm or less, as compared with 76% of women in the study by Robson et al., yet we observed a survival disad-

vantage for carriers of *BRCA1* mutations in women with small tumors.

In a similar study, El-Tamer et al.<sup>13</sup> tested tumor blocks from 487 Jewish women who were treated at the New York Presbyterian Hospital. They found that 51 of the women were mutation carriers (10%), but there were no significant differences in either overall or breast-cancer-specific survival between carriers and noncarriers. The average follow-up period was short (50 months), and the cohort was not divided according to tumor size or the use of chemotherapy. Furthermore, 10 of 31 subjects who carried a *BRCA* mutation had ductal carcinoma in situ.

In a report from a clinic in Rotterdam for patients at high risk for breast cancer,<sup>14</sup> the breast-cancer-specific survival times for carriers of *BRCA1* mutations and noncarriers were similar. The average age at diagnosis in the Dutch study was 39 years; in our study, we observed effects related to the age at diagnosis. Furthermore, hazard ratios in the Dutch study were adjusted for tumor grade and estrogen-receptor status. Such adjustment may be appropriate for testing whether the effect of *BRCA1* mutational status on prog-



**Figure 1.** Breast-Cancer-Specific Survival among Ashkenazi Jewish Women, According to Genetic Subgroup, Tumor Size, and Age at Diagnosis.

The probability of survival at 10 years is shown for women with tumors that were 2 cm or less (Panel A) or more than 2 cm (Panel B) and for women who were less than 50 years old (Panel C) or 50 years or older (Panel D).

nosis is independent of other prognostic factors but can be misleading for women with *BRCA1* mutations who are trying to choose between prophylactic surgery and surveillance.

In our study, subjects were not selected for age, family history, tumor stage, or treatment; these factors may influence survival rates but obscure important underlying differences. There are several other strengths of our study. We were successful in obtaining tumor specimens from 22 of 24 treating hospitals (71% of eligible subjects), and our cohort appeared to be representative of all Israeli women with breast cancer. We were able to genotype all the specimens we had obtained. All subjects had received the diagnosis of breast cancer within a 2-year period and were followed for a minimum of 10 years. Treatment

regimens were relatively homogeneous and were chosen without knowledge of mutational status. Breast cancer was diagnosed in all women in our study before the introduction of mammography<sup>17,18</sup> or genetic testing in Israel, and special surveillance was not offered to women with a family history of cancer. No study subject was aware of her genetic status.

Our study has a number of limitations. Tumor grade and estrogen-receptor status were not routinely recorded. We tested for only the three founder mutations. It is possible that we misclassified some hereditary cases, but the great majority of Jewish women with *BRCA1* and *BRCA2* mutations have one of these three mutations.<sup>19,20</sup> Since we identified only 135 mutation carriers, the subgroup analyses relied on a small number of sub-



jects. The Israel National Cancer Registry captures outcome data on almost all patients with cancer who are treated in Israel, but recurrences and deaths in women after they have emigrated from Israel are not recorded. We had 16-year follow-up data on mortality and incident cancers, but information on the cause of death was available from the Central Bureau of Statistics only for deaths that occurred before 2000. Inherent to the type of study we conducted are the lack of central verification of the pathological diagnosis and incomplete data concerning estrogen-receptor status, information that was retrieved from medical records when it was available. Although we did not see any clear survival differences in association with the *BRCA* mutations we sought, potentially important differences emerged when we ana-

lyzed the data according to tumor size and the use or nonuse of chemotherapy.

Supported by a grant (CA8097) from the National Cancer Institute.

No potential conflict of interest relevant to this article was reported.

We thank the following oncology and pathology units for their help in providing samples from and records of study participants: Ziv Hospital (G. Zaidan), Western Galilee Hospital (Y. Cohen, M. Ben Shahar), Rambam Hospital (O. Ben Izhak, A. Kuten), Bnei Zion Hospital (I. Mislevich, L. Lev), Carmel Hospital (Y. Sova, M. Steiner), Hillel Yafe Hospital (G. Groisman), Meir Hospital (J. Bernheim, Y. Shapira), Beilinson Hospital (E. Okun, A. Sulkes), Hasharon Hospital (B. Klein), Ichilov Hospital (B. Lifshits, M. Inbar), Shiba Hospital (Y. Kopelovich, R. Katan, B. Kaufman), Wolfson Hospital (I. Avinoach, Y. Brenner), Kaplan Hospital (M. Husser, A. Shani), Soroka Hospital (J Goldstien, Y. Cohen), Shaare Zedek Hospital (E. Rosenman, A. Gabizon), Bikur Holim Hospital (G. Lachovizki), Hadassah Hospital (T. Peretz), Haemek Hospital (Y. Honigman), and Dr. M. Bar-Chana of the Israel National Cancer Registry.

## REFERENCES

- Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB, eds. Cancer incidence in five continents. Vol. VII. Lyon, France: IARC Press, 2000. (IARC scientific publications no. 155.)
- Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of *BRCA1* and *BRCA2* among Ashkenazi Jews. *N Engl J Med* 1997;336:1401-8.
- Oddoux C, Struewing JP, Clayton CM, et al. The carrier frequency of the *BRCA2* 6174 delT mutation among Ashkenazi Jewish individuals is approximately 1%. *Nat Genet* 1996;14:188-90.
- Warner E, Foulkes W, Goodwin P, et al. Prevalence and penetrance of *BRCA1* and *BRCA2* gene mutations in unselected Ashkenazi Jewish women with breast cancer. *J Natl Cancer Inst* 1999;91:1241-7.
- Johannsson OT, Idvall I, Anderson C, et al. Tumour biological features of *BRCA1*-induced breast and ovarian cancer. *Eur J Cancer* 1997;33:362-71.
- Karp SE, Tonin PN, Begin LR, et al. Influence of *BRCA1* mutations on nuclear grade and estrogen receptor status of breast carcinoma in Ashkenazi Jewish women. *Cancer* 1997;80:435-41.
- Stoppa-Lyonnet D, Ansquer Y, Dreyfus H, et al. Familial invasive breast cancers: worse outcome related to *BRCA1* mutations. *J Clin Oncol* 2000;18:4053-9.
- Eerola H, Vahteristo P, Sarantaus L, et al. Survival of breast cancer patients in *BRCA1*, *BRCA2*, and non-*BRCA1/2* breast cancer families: a relative survival analysis from Finland. *Int J Cancer* 2001;93:368-72.
- Goode EL, Dunning AM, Kuschel B, et al. Effect of germ-line genetic variation on breast cancer survival in a population-based study. *Cancer Res* 2002;62:3052-7.
- Goffin JR, Chappuis PO, Begin LR, et al. Impact of germline *BRCA1* mutations and overexpression of p53 on prognosis and response to treatment following breast carcinoma: 10-year follow up data. *Cancer* 2003;97:527-36.
- Moller P, Borg A, Evans DG, et al. Survival in prospectively ascertained familial breast cancer: analysis of a series stratified by tumour characteristics, *BRCA* mutations and oophorectomy. *Int J Cancer* 2002;101:555-9.
- Robson ME, Chappuis PO, Satagopan J, et al. A combined analysis of outcome following breast cancer: differences in survival based on *BRCA1/BRCA2* mutation status and administration of adjuvant treatment. *Breast Cancer Res* 2004;6:R8-R17.
- El-Tamer M, Russo D, Troxel A, et al. Survival and recurrence after breast cancer in *BRCA1/2* mutation carriers. *Ann Surg Oncol* 2004;11:157-64.
- Brekelmans CT, Seynaeve C, Menke-Pluymers M, et al. Survival and prognostic factors in *BRCA1*-associated breast cancer. *Ann Oncol* 2006;17:391-400.
- Israel Cancer Registry — 1997. Jerusalem, Israel: Ministry of Health, 2001. (Accessed June 15, 2007, at <http://www.health.gov.il/pages/default.asp?maincat=22>.)
- Kuperstein G, Foulkes WD, Ghadirian P, Hakimi J, Narod SA. A rapid fluorescent multiplexed-PCR analysis (FMPA) for founder mutations in the *BRCA1* and *BRCA2* genes. *Clin Genet* 2000;57:213-20.
- Rennett G. Breast cancer screening in Israel a report to the Director General, Ministry of Health, Israel. Jerusalem, Israel: Ministry of Health, 1999.
- Idem*. Breast cancer in Israel — ethnic peculiarities, influence of immigration, and screening. Presented at the International Epidemiology Association Meeting, Florence, Italy, August 31–September 4, 1999.
- Phelan CM, Kwan E, Jack E, et al. A low frequency of non-founder *BRCA1* mutations in Ashkenazi Jewish breast-ovarian cancer families. *Hum Mutat* 2002;20:352-7.
- Kauff ND, Perez-Segura P, Robson ME, et al. Incidence of non-founder *BRCA1* and *BRCA2* mutations in high risk Ashkenazi breast and ovarian cancer families. *J Med Genet* 2002;39:611-4.

Copyright © 2007 Massachusetts Medical Society.