

Survival After Breast Cancer in Ashkenazi Jewish BRCA1 and BRCA2 Mutation Carriers

Jennifer S. Lee, Sholom Wacholder, Jeffery P. Struewing, Mary McAdams, David Pee, Lawrence C. Brody, Margaret A. Tucker, Patricia Hartge

Background: Studies of survival following breast and ovarian cancers in BRCA1 and/or BRCA2 mutation carriers have yielded conflicting results. We undertook an analysis of a community-based study of Ashkenazi Jews to investigate the effect of three founder mutations in BRCA1 and BRCA2 on survival among patients with breast or ovarian cancer. **Methods:** We collected blood samples and questionnaire data from 5318 Ashkenazi Jewish volunteers. The blood samples were tested for 185delAG (two nucleotide deletion) and 5382insC (single nucleotide insertion) mutations in BRCA1 and the 6174delT (single nucleotide deletion) mutation in BRCA2. To estimate survival differences in the affected relatives according to their BRCA1 and/or BRCA2 mutation carrier status, we devised and applied a novel extension of the kin-cohort method. **Results:** Fifty mutation carriers reported that 58 of their first-degree relatives had been diagnosed with breast cancer and 10 with ovarian cancer; 907 noncarriers reported 979 first-degree relatives with breast cancer and 116 with ovarian cancer. Kaplan–Meier estimates of median survival after breast cancer were 16 years (95% confidence interval [CI] = 11–40) in the relatives of carriers and 18 years (95% CI = 15–22) in the relatives of noncarriers, a difference that was not statistically significant (two-sided $P = .87$). There was also no difference in survival times among the 126 first-degree relatives with ovarian cancer. We found no survival difference between patients with breast or ovarian cancer who were inferred carriers of BRCA1 and/or BRCA2 mutations and noncarriers. **Conclusions:** Carriers of BRCA1 and BRCA2 mutations appeared to have neither better nor worse

survival prognosis. [J Natl Cancer Inst 1999;91:259–63]

Studies (1–8) examining the role of BRCA1 and/or BRCA2 germline mutations in survival among patients with breast and ovarian cancers have been small in size and conflicting in their findings. Studies have reported better (6), worse (5), or typical (1–4,8) survival following breast cancer and better (7) or typical (2) survival following ovarian cancer. Studies (1–11) of histology and other prognostic factors have also been conflicting.

More than 400 protein-truncating mutations in the BRCA1 and BRCA2 genes have been characterized.¹ This wide range of mutations and the lack of functional assays have made determination of cancer survival among BRCA1 and/or BRCA2 mutation carriers difficult. In the Ashkenazi Jewish population, characteristic BRCA1 and BRCA2 mutations have been identified; therefore, within this population, a relatively large number of mutation carriers can be identified more efficiently to estimate survival after cancer.

In the Ashkenazi Jewish population, two BRCA1 mutations, 185delAG (two nucleotide deletion) and 5382insC (single nucleotide insertion), and one BRCA2 mutation, 6174delT (single nucleotide deletion), have a combined frequency exceeding 2% (12–14). Recently, a large community-based survey (15) of this population obtained family history data from participants who were subsequently tested for BRCA1 and BRCA2 mutations. This study investigates the effect of BRCA1 and/or BRCA2 mutations on survival among patients with breast and ovarian cancers.

SUBJECTS AND METHODS

Subjects and Data Collection

Recruitment of volunteers from the community-based survey, collection of data, and laboratory methods have been described in detail elsewhere (15). Briefly, 5318 Jewish men and women over the age of 20 years were recruited from the Washington, DC, area. After giving written informed consent, participants gave blood samples and completed a self-administered questionnaire. Polymerase chain reaction (PCR)-based assays on blood samples were performed to determine carrier status for two BRCA1 mutations, 185delAG and 5382insC, and one BRCA2 mutation, 6174delT. Positive mutation carrier status was defined by detection of either a BRCA1 or BRCA2 mutation. Only samples that were positive on at least two independent PCR-based assays were considered positive in the statis-

tical analyses. The questionnaire elicited information on the participants' first-degree relatives, namely, history of cancer, including type(s) of cancer, age at diagnosis, and survival status. This project proposal was performed after approval by the institutional review board of the National Cancer Institute, Bethesda, MD.

Statistical Methods

We calculated follow-up time from diagnosis of cancer to date of death (from any cause) or, for those alive, we censored follow-up at the date of questionnaire completion. Individuals were excluded from the analyses if such data were missing and thus follow-up was unknown.

We analyzed survival difference in two ways. First, we estimated survival curves in the affected relatives of carriers and the affected relatives of noncarriers, overall and within strata defined by age at and calendar period of diagnosis. We estimated survival curves by using the Kaplan–Meier technique (16), compared survival curves using the two-sided logrank test (17) and the Cox proportional hazards model, and considered P values below .05 as statistically significant. This qualitative approach would reveal any marked differences in survival among carriers if one existed, even though we knew the BRCA1 and/or BRCA2 carrier status only of the study participants, not of their affected relatives.

The second survival analysis applied a more quantitative approach (see Appendix). We extended the kin-cohort method to infer the prevalence of BRCA1 and/or BRCA2 mutations in first-degree relatives of carriers and noncarriers, specific for age at diagnosis (15,18). With the use of estimates of age-specific penetrance from our previous report (15), we inferred the proportions of mutation carriers and noncarriers in these two groups of patients. A large proportion of affected relatives of mutation carriers are carriers themselves; by contrast, only a small minority of affected first-degree relatives of noncarriers are (or were) themselves carriers, since so few (<3%) of the general Ashkenazi Jewish population are BRCA1 and/or BRCA2 mutation carriers (15). We then fitted linear regression models, including terms for age at diagnosis, calendar period of diagnosis, and the related participant's mutation carrier status (19). From this, we determined and compared maximum likelihood estimates for survival after breast cancer among the inferred BRCA1 and/or BRCA2 mutation carriers and noncarriers.

Affiliations of authors: J. S. Lee, Howard Hughes Medical Institute, Bethesda, MD, and Division of Cancer Epidemiology and Genetics, National Cancer Institute (NCI), Bethesda; S. Wacholder, J. P. Struewing, M. A. Tucker, P. Hartge, Division of Cancer Epidemiology and Genetics, NCI; M. McAdams, D. Pee, Information Management Services Inc., Silver Spring, MD; L. C. Brody, Genetics and Molecular Biology Branch, National Human Genome Research Institute, Bethesda.

Correspondence to: Patricia Hartge, Sc.D., National Institutes of Health, Executive Plaza North, Rm. 443, Bethesda, MD 20852 (e-mail: hartge@nih.gov).

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Because of small numbers, we used only the first method for ovarian cancer. *P* values given are from two-sided tests.

RESULTS

In total, 957 participants reported 1037 female first-degree relatives with breast cancer (Table 1). Most participants reported only one affected first-degree relative; the vast majority of the 1037 affected first-degree relatives were not related to one another. Specifically, 72% of those reported by mutation carriers and 86% of those reported by noncarriers were not related to one another; the remainder was comprised of mostly related pairs and a few related triples. Among the 58 affected relatives reported by the mutation carriers, four (7%) were reported to have been diagnosed with ovarian cancer while another four had been diagnosed with a different additional type of cancer. No relationship between the type of additional cancer and the specific mutation was apparent. Among the 979 affected relatives reported by the noncarriers, 155 (16%) were reported to have one of several cancer types, of which no one predominated.

Overall survival after breast cancer did not differ significantly between the first-degree relatives of BRCA1 and/or BRCA2 mutation carriers and those of the noncarriers (Table 2). Fig. 1 shows Kaplan-Meier survival curves for affected first-degree relatives of carriers and noncarriers. First-degree relatives of mutation carriers tended to be diagnosed with breast cancer at a younger age and in earlier years than relatives of noncarriers. Five-year survival rates were similar for affected first-degree

Table 1. Characteristics of first-degree relatives with breast cancer

BRCA1 and/or BRCA2 mutation carrier status of participants	First-degree relatives with breast cancer		
	Type of first-degree relative	Mean age at diagnosis, y (range)	Mean age at study entry or death, y (range)
Carriers (n = 50)	58 first-degree relatives reported	47 (26-74)	59 (28-93)
	42 unrelated to one another		
	8 related pairs		
	41 mothers	49 (32-74)	62 (36-93)
Noncarriers (n = 907)	17 sisters	41 (26-58)	51 (28-82)
	979 first-degree relatives reported	56 (25-90)	67 (27-96)
	841 unrelated		
	60 related pairs and 6 related triples		
	693 mothers	58 (25-90)	70 (27-96)
	263 sisters	52 (28-90)	61 (31-91)
	23 daughters	39 (27-53)	42 (31-56)

relatives of carriers (74%) and those of noncarriers (78%). Ten-year survival rates were also similar for the two groups.

To adjust for the effects of age and year at diagnosis, we fitted a Cox proportional hazards regression model. The hazard's ratio estimate comparing carriers' and noncarriers' first-degree relatives with breast cancer was 1.04 (95% confidence interval [CI] = 0.70-1.55). Findings did not differ when we repeated analyses using only mothers of mutation carriers (n = 41) and noncarriers (n = 693).

We examined the effects of specific mutations. Of the 58 affected relatives of mutation carriers, 35 (60%) were reported by participants carrying a BRCA1 mutation and 23 (40%) were reported by participants carrying a BRCA2 mutation. The 5-year survival rate for relatives of carriers of BRCA1 mutations was 79% compared with 65% for BRCA2, a differ-

ence that was not statistically significant. Likewise, the survival times for relatives of 5382insC, 185delAG, and 6174delT mutation carriers did not differ significantly, with or without adjustment for age and year of diagnosis.

Table 3 shows survival estimates of first-degree relatives with breast cancer according to their inferred mutation status. Adjusting for age at and calendar period of diagnosis, we estimate that carriers had a 5% survival advantage at 5 years (95% CI = -12% to 22%) and a 4% advantage at 10 years (95% CI = -15% to 22%). These small differences were not statistically significant.

Ovarian cancer in relatives was reported far less frequently than breast cancer. Of the 126 relatives with ovarian cancer (mean age at diagnosis, 56 years), 10 (8%) were reported by nine BRCA1 and/or BRCA2 mutation carriers and 116 (92%) were reported by 112 noncarriers. No carrier or noncarrier reported more

Table 2. Unadjusted overall survival time by potential prognostic variables for first-degree relatives with breast cancer

	First-degree relatives with breast cancer				<i>P</i> † (logrank test)
	No. of patients	No. of deaths	Unadjusted median survival, y (95% CI)*	Unadjusted mean survival, y (95% CI)*	
Age at diagnosis, y					
<45	238	120	22 (16-30)	27.2 (23.1-31.4)	
45-54	265	104	29 (25-34)	25.4 (23.0-27.8)	
≥55	534	242	11 (10-14)	14.9 (13.6-16.2)	.0001
Year of diagnosis					
<1980	468	321	16 (13-20)	22.5 (20.1-24.9)	
≥1980	540	116	—‡	11.0 (10.6-11.5)	.002
BRCA1 and/or BRCA2 mutation carrier status of participants					
Carriers	58	28	16 (11-40)	20.7 (15.9-25.6)	
Noncarriers	979	438	18 (15-22)	22.8 (20.6-25.0)	.872

*95% CI = 95% confidence interval.

†Two-sided *P* values.

‡More than 50% estimated survival at study date.

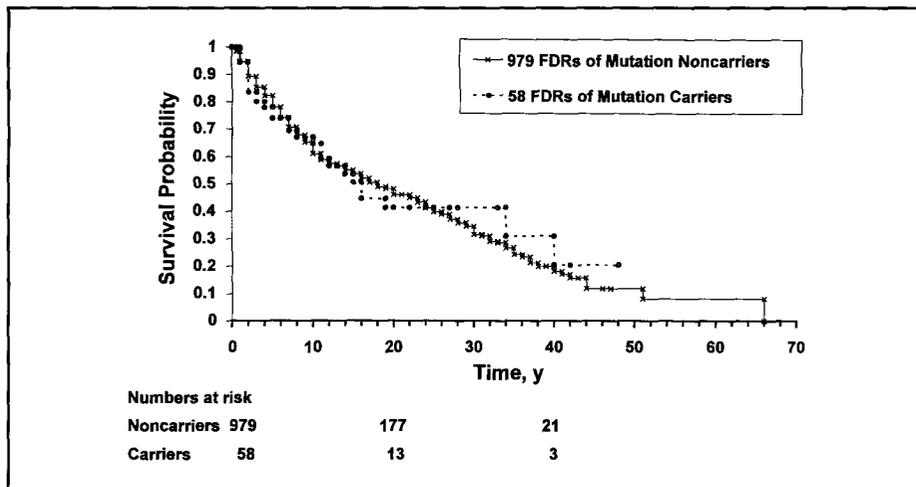


Fig. 1. Overall survival after breast cancer among first-degree relatives (FDRs) of BRCA1 and/or BRCA2 mutation carriers and among first-degree relatives of noncarriers. Numbers of patients at risk at 0, 20, and 40 years are shown below the x-axis. The survival probabilities at 20 and 40 years (plus 95% confidence intervals) are 46% (42%–50%) and 18% (14%–24%), respectively, for noncarriers and 41% (27%–57%) and 21% (7%–50%), respectively, for carriers.

than two first-degree relatives with ovarian cancer. Longer survival after diagnosis of ovarian cancer was strongly related to younger age at diagnosis ($P < .002$) but not significantly related to year of diagnosis or BRCA1 and/or BRCA2 mutation status.

DISCUSSION

Our findings suggest that women with breast cancer who carry any of the three specific BRCA1 and BRCA2 mutations do not have a better or worse survival prognosis than other women with breast cancer. We observed no overall survival difference between affected first-degree relatives of BRCA1 and/or BRCA2 mutation carriers and those of noncarriers. We extended the kin-cohort method (18) to allow us to infer the survival in carriers and noncarriers who were not tested but whose relatives have known genotype.

With the use of this extension, we found no difference in survival after breast cancer between carriers and noncarriers.

Our survival rates and comparisons agree generally with two small studies of Jewish women by Haas et al. (3) and by Robson et al. (4). Our findings also agree with several studies (1,2,8) of patients with breast cancer not limited to those of Jewish descent. Marcus et al. (8) found no survival difference among 90 patients with BRCA1 mutations and 85 patients with no mutations in BRCA1. Verhoog et al. (2) and Johannsson et al. (1) found no differences between BRCA1 mutation-positive patients ascertained from cancer-prone families and sporadic patients from cancer registries. In contrast, other small studies have suggested that BRCA1 and/or BRCA2 mutation carrier status affects survival time (5,6), but small study size, genetic tests in paraffin-embedded tu-

mors, and potential screening biases complicate their interpretation.

Ovarian cancer survival has been difficult to assess, but two relatively small studies (1,7) have reported survival comparisons according to BRCA1 and/or BRCA2 mutation carrier status among patients with ovarian cancer. Johannsson et al. (1) reported an equal or worse survival for 33 patients with BRCA1 mutation-positive ovarian cancer identified from 21 Swedish breast cancer-prone families compared with 97 age- and stage-matched patients with ovarian cancer from the general population, a finding similar to ours. On the other hand, Rubin et al. (7) observed a survival advantage for patients with BRCA1 mutation-positive ovarian cancer compared with sporadic cancer control subjects.

The major limitation of this study was the lack of data about the cause of death in the affected first-degree relatives. If BRCA1 and/or BRCA2 mutations play an etiologic or a prognostic role in diseases other than breast or ovarian cancer that are prevalent in our cohort of first-degree relatives, competing risks may affect our survival comparisons. Mortality from causes other than breast or ovarian cancer after age 60 years appears higher among first-degree relatives of mutation carriers than among those of noncarriers. In addition, other non-BRCA mutations that may affect survival may be present in our study population. It was not possible to ascertain information on histopathologic factors and their effect on survival in our study.

A second limitation of our data is that diagnosis and vital status in the first-degree relatives were not confirmed, but it has been shown that research subjects accurately report family history of common cancers, including breast cancer

Table 3. Linear regression maximum likelihood estimates (MLEs) for survival among first-degree relatives with breast cancer based upon their inferred BRCA1 and/or BRCA2 mutation carrier status, adjusted for age at diagnosis and calendar period of diagnosis

Inferred status first-degree relatives with breast cancer						
Age at diagnosis, y	Year of diagnosis	Total No. of carriers and noncarriers (n = 1008)†	No. of carriers (n = 82) (row %)	No. of noncarriers (n = 926) (row %)	MLE 5-y survival rate (95% CI)*	
					Breast cancer carriers	Breast cancer noncarriers
<45	<1980	154	36 (23)	118 (73)	0.73 (0.57–0.85)	0.78 (0.71–0.84)
	≥1980	78	17 (22)	61 (78)	0.85 (0.64–0.95)	0.90 (0.80–0.95)
45–54	<1980	149	11 (7)	138 (93)	0.75 (0.55–0.88)	0.81 (0.75–0.85)
	≥1980	109	8 (7)	101 (93)	0.87 (0.60–0.97)	0.93 (0.86–0.96)
≥55	<1980	165	3 (2)	162 (98)	0.70 (0.50–0.84)	0.75 (0.70–0.80)
	≥1980	353	7 (2)	346 (98)	0.81 (0.59–0.93)	0.87 (0.83–0.90)

*95% CI = 95% confidence interval.

†Twenty-nine subjects missing year of diagnosis included.

(20). In addition, substantial bias from inaccurate reporting by participants about their first-degree relatives seems remote, since participants in our study were generally well educated (>57% had postgraduate education) (15). Furthermore, any inaccuracies are not likely to be related to the observed carrier status of participants or the inferred carrier status of their affected first-degree relatives. We adjusted for age at and year of diagnosis to avoid possible confounding from potential differences in cancer staging and treatment.

This study avoided several of the common sources of bias that can hamper survival studies that compare hereditary breast or ovarian cancer to patient groups ascertained from different sources. For example, comparing BRCA1 and/or BRCA2 mutation-positive patients from cancer-prone families (1,2,6,8) or hospitals (7) to sporadic cancer patients from cancer clinics (7) or cancer registry (1,2,6,8) offers potential for bias in estimating survival. Patients from cancer clinics or cancer-prone families selected for gene mapping studies may be more likely to be diagnosed earlier through more rigorous screening and to be alive for study involvement. Such screening biases could operate in the present study, but to a lesser extent since most carriers lacked extensive family history of cancer. Evaluating individuals from families selected for linkage analysis also may bias findings toward longer survival time among BRCA1 and/or BRCA2 mutation-positive patients because such families likely have multiple living affected members. Selecting sporadic cancer patients from cancer clinics or hospitals may underestimate survival time in the comparison group of possibly more advanced stages of cancer. In addition, ascertaining a control group of patients from such sources or from a cancer registry does not involve direct BRCA1 or BRCA2 mutation testing.

Other strengths of this study include the study subjects' lack of awareness of their mutation status, the large sample size, and relative genetic homogeneity. Our study population consisted of volunteer Ashkenazi Jews in the Washington, DC, area. More participants had a positive family history of breast or ovarian cancer than would be expected (15). We know of no reasons for volunteering to be related to both BRCA1 and/or BRCA2 mutation carrier status and survival time or for fam-

ily history, timing of cancer detection, and treatment to favor one survival comparison group over the other in our study. Survival studies of heterogeneous populations include numerous BRCA1 and BRCA2 mutations; in contrast, this community-based study of Ashkenazi Jews compares survival among individuals who differ at one of only three specific BRCA1 and BRCA2 mutation sites.

While the exact functions of the BRCA1 and BRCA2 genes remain elusive (21), the potential effect of mutations in these genes on survival among cancer patients has important clinical and screening implications. Our results from a community-based study suggest that BRCA1 and/or BRCA2 mutation carrier status does not have a major impact on overall survival time among patients with breast or ovarian cancer. Thus, screening for BRCA1 and/or BRCA2 mutations does not contribute prognostic information about survival among women with breast or ovarian cancer.

APPENDIX

From our study data, we can directly estimate cumulative survival after diagnosis of breast cancer in affected first-degree relatives of carriers and affected first-degree relatives of noncarriers. We can translate these survival functions into cumulative survival in affected carriers and affected noncarriers themselves. To do this, we view as mixtures of carriers and noncarriers the two cohorts of women diagnosed with cancer in a given age interval: the affected first-degree relatives of carrier participants and the affected first-degree relatives of noncarrier participants. The directly estimable survival rates in these two cohorts are weighted averages of the survival rates in affected carriers and affected noncarriers. The weight for the carriers in each of the two cohorts is simply the proportion of carriers in the cohort. This can be calculated from the Mendelian probability that a first-degree relative of an individual with known genotype is herself a carrier and the probability of being diagnosed with breast cancer, given carrier status. By solving two equations in two unknowns, we can then infer the survival rates in carriers and noncarriers with breast cancer.

This is the same basic approach we took in estimating penetrance in other reports from this study (15,18). The main difference is that the outcomes in those studies were incidence of cancer so the (retrospective) follow-up in those cohorts began at birth; therefore, the weights depended only on the Mendelian probabilities. Here, on the other hand, the outcome is death after diagnosis with breast cancer. Therefore, the weights are the fractions of

carriers in the two cohorts of affected relatives (that is, those of carriers and those of noncarriers) who were diagnosed during the age interval t_{i-1} to t_i . By applying rules of conditional probability, we calculated the weights as the product of the probability of the relative being born a carrier, given the participant's genotype, obtained from Mendelian principles (15,18), and the probability of the relative developing cancer during age interval t_{i-1} to t_i , given the participant's genotype (b_i^+ for carriers or b_i^- for noncarriers). Here, b_i^+ can be calculated as $b_i^+ = B_i^+ - B_{i-1}^+$, where B_i^+ is cumulative probability of developing cancer through interval i in carriers (15); b_i^- can be obtained analogously. By assuming that censoring due to death from other causes before the diagnosis of cancer is independent of carrier status, we can calculate the proportion of carriers among the carrier participants' first-degree relatives diagnosed during interval i as

$$C_i^+ = \frac{(p/2 + 1/2)b_i^+}{(p/2 + 1/2)b_i^+ + (1/2 - p/2)b_i^-} \quad [1]$$

and, analogously the weight for affected carriers among the noncarrier participants' first-degree relatives diagnosed during interval i as

$$C_i^- = \frac{pb_i^+}{pb_i^+ + (1-p)b_i^-}, \quad [2]$$

where p is the mutant allele frequency in the study population.

The probability of survival through year j , after diagnosis during interval i , among affected first-degree relatives of carriers can be expressed as

$$A_{ij}^+ = C_i^+ S_{ij}^+ + (1 - C_i^+) S_{ij}^-, \quad [3]$$

where S_{ij}^+ and S_{ij}^- are the probabilities of survival through year j among affected carriers and noncarriers, respectively, who were diagnosed during interval i . Similarly, the probability of survival through year j , after diagnosis during interval i , among affected first-degree relatives of noncarriers can be expressed as

$$A_{ij}^- = C_i^- S_{ij}^+ + (1 - C_i^-) S_{ij}^-. \quad [4]$$

By solving Equations 3 and 4 for two unknowns, we can express S_{ij}^+ and S_{ij}^- for fixed j as

$$S_{ij}^+ = \frac{(1 - C_i^-) A_{ij}^+ - (1 - C_i^+) A_{ij}^-}{C_i^+ - C_i^-} \quad [5]$$

and

$$S_{ij}^- = \frac{C_i^+ A_{ij}^- - C_i^- A_{ij}^+}{C_i^+ - C_i^-} \quad [6]$$

in terms of quantities estimable from our data.

We assumed a frequency $P = .0112$ for any of the three specific alleles in our study in order to estimate C_i^+ and C_i^- . To estimate A_{ij}^+ and A_{ij}^- from Equations 5 and 6, we used Kaplan-Meier estimates for probability of survival after diagnosis among the affected relatives of carriers and of noncarriers, respectively, based on our data (Fig. 1).

The 5- and 10-year survival probabilities for carriers and noncarriers for all ages at diagnosis were approximated using binomial regression. The two binomial variables for each interval i corresponded to the groups of affected relatives of carriers and noncarriers, respectively. The binomial numerators were the numbers of deaths during interval j ; the denominators were the differences between the number of women in the groups during the interval j and half the number of censored in the groups during the interval j . A model with identity link (19) was fitted with regression variables A_{ij}^- and A_{ij}^+ for relatives of carriers and noncarriers, respectively, and unknown regression coefficients S_{ij}^+ and S_{ij}^- .

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NOTES

¹Breast Cancer Information Core site http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic/

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