

Breast Cancer Risk in Ashkenazi BRCA1/2 Mutation Carriers: Effects of Reproductive History

Patricia Hartge,¹ Nilanjan Chatterjee,¹ Sholom Wacholder,¹ Lawrence C. Brody,² Margaret A. Tucker,¹ and Jeffery P. Struwing³

Background. Younger age at first birth and greater parity generally reduce the risk of developing breast cancer, but whether this reduced risk holds in women with a mutation in the BRCA1 or BRCA2 gene is unknown.

Methods. In a Washington DC community-based study conducted in 1996, we tested 5318 Ashkenazi Jews for three BRCA1/2 founder mutations and identified 120 mutation carriers. Applying an extension of the "kin-cohort" analysis, we compared the effects of reproduction on breast cancer risk in carriers and noncarriers. We also used a case-case analysis among 288 participants who had been diagnosed with breast cancer.

Results. In noncarriers, the estimated relative risk (RR) of breast cancer rose 5% with each 5-year increment in age at first

birth (RR = 1.05; 95% confidence interval [CI] = 0.97–1.15). By contrast, the estimated risk in mutation carriers fell with each 5-year increment in age (RR = 0.65; 95% CI = 0.37–1.16). Among the 288 participants who were breast cancer survivors themselves, the comparison of carriers with noncarriers also showed no protection associated with early birth in the presence of a mutation in BRCA1 or BRCA2.

Conclusions. It is not yet clear whether the recognized breast cancer risk factors operate in the same way in women who carry a mutation in the BRCA1 or BRCA2 genes. (EPIDEMIOLOGY 2002;13:255–261)

Key words: breast cancer, BRCA1/2 mutation, reproduction, epidemiology.

It is well established that women who first give birth at younger ages have lower risk of developing breast cancer,^{1,2} but it is not clear whether this protection holds among women whose risk is dramatically increased because they carry mutations in the BRCA1 or BRCA2 genes. Indeed, it is difficult to address the issue in epidemiologic studies because of the rarity of the mutations. Selected families in clinics that care for high-risk women provide some data, but it is not certain how widely this applies to the total population of carriers.^{3–5}

One challenge for epidemiologic research in the overall population of carriers is that more than 1000 different mutations in the BRCA1 and BRCA2 genes have been characterized. This wide range of mutations and the lack

of functional assays have made detection of the BRCA1/2 mutation carriers in the general population costly and difficult. In the Ashkenazi Jewish population, founder BRCA1 mutations in BRCA1 (185delAG and 5382insC) and BRCA2 (6174delT) have a combined frequency exceeding 2%,^{6–8} and so a relatively large number of BRCA1/2 mutation carriers can be identified more efficiently to study risk in BRCA1/2 carriers. To estimate cancer risk in carriers, we conducted a large community-based survey of Ashkenazi Jews and obtained family history data from participants, who were subsequently tested for BRCA1/2 mutations.⁹

The present analysis investigates the effects of non-genetic risk factors that may interact with BRCA1/2 mutations to influence risk of developing breast cancer. We used the kin-cohort technique to derive unbiased estimates of the age-specific cancer risks in subgroups defined by reproductive history.

Methods

We have previously described the recruitment of volunteers from the community-based survey, collection of data, and laboratory methods.^{9,10} Briefly, in 1996, we

From the ¹Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, ²Genetics and Molecular Biology Branch, National Cancer Institute, Bethesda, MD, and ³Center for Cancer Research, National Cancer Institute, Bethesda, MD.

Address correspondence and reprint requests to: Patricia Hartge, Sc.D., National Cancer Institute, EPS 8090, 6120 Executive Blvd., Bethesda, MD 20892-7246; e-mail: hartgep@exchange.nih.gov

Submitted 31 May 2001; final version accepted 8 January 2002.

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recruited 5318 Jewish men and women over the age of 20 from among the estimated 150,000 Jewish persons in the Washington DC area, using notices in newspapers, radio, posters, and publicity in such places as community centers, synagogues, and Jewish organizations. Subjects were enrolled over a 9-week period at 15 study sites. This study was approved by an institutional review board of the National Cancer Institute, Bethesda, Maryland.

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 BRCA1/2 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 statistical analyses.

The questionnaire elicited information on the participants' first-degree relatives, namely year of birth, year of death if deceased, and history of cancer including type(s) of cancer and age at diagnosis. The mother's age at first birth and total number of live births thus could be inferred. For sets of siblings who participated in the study, each mother was counted only once. We considered her to be the mother of a carrier if any of her children was found to carry a mutation and the mother of noncarriers otherwise.

We measured the interaction of BRCA genes and the potential reproductive modifiers (age at first birth and parity) in two distinct analyses using independent data. The first, an extension¹⁰ of the kin-cohort approach¹¹ used in this and later studies,^{12,13} used data from the mothers of all of the 5318 study participants but not from participants themselves. The second approach, a case-case analysis,¹⁴ used data from participants themselves, specifically those participants who reported having been diagnosed with breast cancer.

In the main kin-cohort analysis, we estimated the age-specific cumulative risk of disease using a maximum likelihood method.¹⁰ The method exploits the fact that more than 97% of Ashkenazi Jews in the United States are BRCA1/2 non-carriers, so the vast majority of mothers of noncarriers are noncarriers, too, whereas slightly more than 50% of all mothers of BRCA1/2-positive participants are carriers themselves. This information can be used to construct a marginal likelihood of observing each individual relative's disease history data given the mutation status of the corresponding participants. Estimates of the age-specific cumulative risk for carriers and noncarriers can be obtained by maximizing this likelihood.

We used this maximum likelihood method to analyze the disease history data of the mothers stratified by their age at first birth (<25, 25–30, >30) or their parity (1–2,

3+) to estimate the age-specific cumulative risk of breast cancer in carriers and noncarriers according to reproductive history. To estimate relative risk (RR) associated with age at first birth or parity categories or to investigate the effects of age at first birth or parity as continuous variables, we considered separate (stratified) proportional hazard models for noncarriers and carriers. The maximum likelihood approach was again used to estimate the parameters of this model from the genotype data of the participants and the mothers' disease and reproductive history data (Appendix).

Second, we used a case-case approach to make comparisons within the group of 288 women who participated in the study and reported that they had been diagnosed with breast cancer. Neither absolute cancer risk nor RR associated with age at first birth, for example, can be estimated from a case-case analysis, but interaction between genotype and age at first birth can be estimated under certain assumptions.¹⁴ We made three assumptions to estimate interaction odds ratio from the case-case analysis. First, we made the usual case-case assumption that BRCA1/2 genotype is independent of reproductive history. Second, we assumed that survival in this population did not depend on genotype or reproductive risk factors. It has already been demonstrated that carriers and noncarriers had similar breast cancer survival odds.¹⁵ Third, we assumed that volunteering for this study did not depend on reproductive history *differently* in carriers and noncarriers.

Results

Out of 5318 study participants, 120 carried one of the founder mutations. After accounting for siblings who participated, there were 117 mothers of carriers (60 with BRCA1 and 57 with BRCA2 mutations) and 5094 mothers of noncarriers available for analysis (Table 1). On average, the mothers of carriers were younger, more of them had their first child before they were 25 years old, and fewer of them had more than three children. More of them had developed breast cancer or ovarian cancer, which would be predicted because half of them would be expected to carry a mutation themselves.

We classified all of the female subjects in the study by decade of birth, parity and age at first birth (among the parous women), and carrier status. Given decade of birth, parity and age at first birth were virtually identical in carriers and noncarriers.

Among mothers of noncarriers, those who first gave birth at older ages were more likely to have developed breast cancer (Table 2). The trend was relatively smooth and statistically important, rising from 10% to 18%. On the other hand, the mothers of mutation carriers showed no evidence of the typical relation between later age at first birth and increased risk of breast cancer. The num-

TABLE 1. Mothers of Study Participants, According to Participants' Mutation Status

	Study Participant Mutation Status			
	BRCA1	BRCA2	BRCA1/2	None
Mother's year of birth (%)				
<1910	17	23	20	31
1910-1919	35	25	30	24
1920-1929	27	25	26	23
1930-1939	12	16	14	12
1940 or later	2	7	4	6
Unknown	8	5	7	5
Parity (%)				
1 birth	7	12	9	9
2 births	48	47	48	44
3 births	28	35	32	30
4 or more births	17	5	11	17
Mother's age at first birth (%)				
<25	45	42	43	38
25-29	30	30	29	39
30-34	15	16	15	13
35+	2	7	4	4
Unknown	8	5	7	5
Mother's breast cancer history (%)				
No	58	67	62	83
Yes	38	32	35	14
Unknown	3	2	3	2
Mother's ovarian cancer history (%)				
No	90	89	90	96
Yes	7	9	8	2
Unknown	3	2	3	2
Offspring (study participant) (%)				
Male	20	28	24	30
Female, history of breast cancer	25	19	22	5
Female, no breast cancer	55	53	54	65
Total number	60	57	117	5094

bers of carriers made the estimates somewhat imprecise, but those mothers of carriers who first gave birth in their thirties actually were less likely to have breast cancer than their peers who had children in their twenties. The patterns were similar for BRCA1 compared with BRCA2 (data not shown).

The association of parity with breast cancer also differed for mothers of carriers and noncarriers (Table 2). Among the noncarriers' mothers, breast cancer risk fell from 16% to 12% with increased numbers of births.

No such pattern was seen in carriers' mothers, either overall (Table 2) or stratified by affected gene (data not shown).

Because about half of the mothers of carriers carried no mutation, the absolute cancer risks in the mothers of carriers are intermediate between the risks in carriers and noncarriers. These risks can be estimated by applying the kin-cohort method^{10,11} to the data from the mothers, as shown in Figure 1. In carriers, the risk curves are lowest for women who give birth at older ages.

Table 3 presents the projected risks of breast cancer by decade of life for carriers and noncarriers. The overall hazard ratios in noncarriers, corresponding to the year-by-year data presented in Figure 1, were 1.0 (ref), 1.15, and 1.25 for younger, intermediate, and older first births, respectively. By contrast, the hazard ratios were 1.0 (ref), 0.58, and 0.28 in the carriers. The corresponding multiplicative interaction coefficients were 1.0, 0.50 [95% confidence interval (CI) = 0.18-1.36], and 0.23 (95% CI =

0.06-0.85). To increase the statistical power, age at first birth was also considered as a continuous variable. On average, each 5-year increase in the age at first birth in noncarriers corresponded to a 5% increase in breast cancer risk (RR per 5 years = 1.05; 95% CI = 0.96-1.15). By contrast, each 5-year increase in age at first birth among carriers corresponded to a 35% decrease (RR per 5 years = 0.65; 95% CI = 0.37-1.15). The corresponding multiplicative interaction coefficient was 0.62 (95% CI = 0.35-1.12).

TABLE 2. Proportion of Mothers with Breast Cancer, by Mutation of the Offspring and Age at First Birth or Parity of the Mother

	Offspring with BRCA1/2 Mutations		No Mutations in Offspring	
	Percent with Breast Cancer	Total Women	Percent with Breast Cancer	Total Women
Mother's age at first birth				
<20	0	2	10	191
20-24	40	48	13	1726
25-29	40	35	15	1971
30+	30	23	18	864
Trend test*	P = 0.95†		P = 0.0003	
Mother's total number of children				
1	30	10	16	413
2	33	52	16	2138
3	46	35	14	1457
4+	36	11	12	754
Trend test*	P = 0.68		P = 0.02	

* Adjusted for year of birth; † age < 20 combined with 20-24.

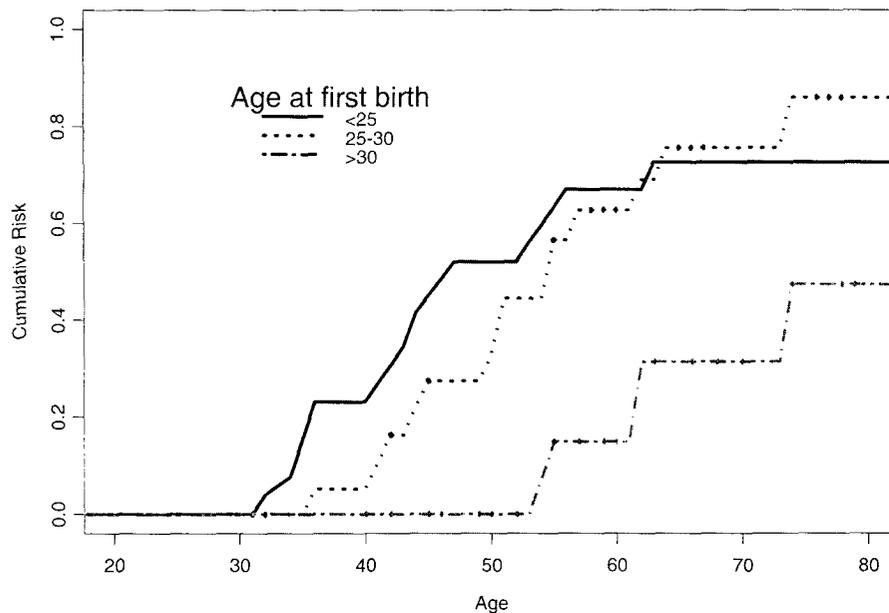


FIGURE 1. Age-specific risk of breast cancer in BRCA1/2 mutation carriers by age at first birth, estimated from mother's cancer history and participant's mutation status.

We also assessed the effect of parity on the risks of breast cancer in carriers and in noncarriers, controlling for age at first birth, using both categorical and continuous versions of parity (data not shown). Among the noncarriers, women who had three or more births showed a slightly lower risk of breast cancer in comparison with those who had one or two births (RR = 0.90; 95% CI = 0.76–1.08). Among the carriers, the association was reversed. Carriers with three or more births had a higher risk of breast cancer than their peers with one or two births (RR = 2.13; 95% CI = 0.83–5.51). The corresponding interaction between parity and carrier status was 2.36 (95% CI = 0.87–6.43). If the number of births is treated as a continuous variable, the noncarriers show a 5% reduction in risk per additional birth (RR = 0.95; 95% CI = 0.87–1.04). Among the carriers, by contrast, risk increases by 26% with each additional birth (RR = 1.26; 95% CI = 0.73–2.16). The

multiplicative interaction in the continuous model was 1.33 (95% CI = 0.76–2.33).

Table 4 presents data from the 288 study participants who reported that they had been diagnosed with breast cancer, comparing carriers with noncarriers in a case-case analysis. If younger age at first birth were equally protective in carriers and noncarriers, then the interaction odds ratios would be 1.0. Instead, the carriers were more likely to have early first birth. That is, the association of earlier birth and lower risk was apparently absent or reversed among the carriers. The interaction odds ratios for BRCA mutations and parity did not form a consistent pattern.

Discussion

These findings suggest that earlier first birth may not offer the usual protection against breast cancer in women who inherit a mutation in the BRCA1 or the BRCA2 gene. In particular, Jewish Ashkenazi women carrying one of three founder mutations did not show the inverse association between age at first birth and breast cancer risk that appeared in the Ashkenazi noncarriers and that appears in populations around the world.^{1,2} The two BRCA1 mutations studied are far apart on the gene, and there is little reason to expect effects of other mutations in these genes to differ. Both mutations, like the majority of reported mutations, lead to truncation of the protein before the carboxyl terminal BRCT domain.

TABLE 3. Cumulative Risk of Breast Cancer* at Selected Ages, According to Age at First Birth and Genotype

Age at First Birth	Cumulative Risk of Breast Cancer at Age					Relative Risk†	95% CI
	40	50	60	70	80		
Non-carriers							
<25‡	.013	.049	.081	.115	.143	1.0	
25–29	.015	.038	.077	.123	.168	1.15	0.96–1.38
30+	.009	.039	.075	.120	.182	1.25	1.01–1.55
Carriers							
<25‡	.221	.498	.642	.695	.695	1.0	
25–29	.049	.308	.587	.706	.805	0.58	0.22–1.49
30+	.000	.000	.149	.315	.475	0.28	0.08–1.01

* From kin-cohort analysis.

† Overall hazard ratio for all ages.

‡ Reference category.

TABLE 4. Case-Case Analysis of 288* Study Participants with a History of Breast Cancer

	Carriers	Non-Carriers	Interaction OR†	95% CI
Age at first birth				
<25‡	8	77	1.0	
25–29	8	86	0.7	0.3–2.1
30+	4	55	0.5	0.1–1.9
No births	5	42	0.7	0.2–2.6
Trend test			P = 0.52	
Parity (no. of births)				
No births‡	5	42	1.0	
1	1	34	0.3	0.03–2.6
2	15	104	1.4	0.5–4.3
3+	4	80	0.6	0.2–2.6
Trend test			P = 0.94	

* Three survivors lacked data on parity or age at first birth.

† Odds ratio adjusted for decade of birth.

‡ Reference category.

Strengths of this study included the community base, the study participants' lack of awareness of their mutation status, the large sample size, and relative genetic homogeneity.

Compared with the general U.S. population, the Jewish population has elevated prevalence of breast cancer. The participants in this community survey were more likely to have personal or family history of breast cancer than the whole Jewish population of Washington DC. This selection effect tends to raise the absolute risks in each subset but does not distort the within-study comparison of carriers vs noncarriers. In noncarrier women, the estimated incidence rates of breast cancer are slightly inflated, but the RR associated with advancing age at first birth showed the typical pattern observed in populations around the world. Similarly, the absolute risks in carriers have some upward bias, but the RR associated with age at first birth does not.

Various limitations in the study data could have distorted the findings, including random variation, because the study included only 120 carriers. For the kin-cohort analysis and unadjusted comparisons of mothers, limitations include errors in reporting on mothers' years of birth, death, and any cancer diagnoses. We lacked confirmation of deaths or cancers reported. Also, the kin-cohort approach could not be used to estimate risks in nulliparous women because it relied upon data concerning the study participants' mothers. Some misclassification is inevitable but may have been minimal in this study, in that the expected relation between reproductive history and breast cancer was observed in the noncarriers' data.

Different potential limitations apply to the case-case analyses within the group of 288 breast cancer survivors. A higher proportion of the participants had a positive family history of breast or ovarian cancer than would be seen in a random population sample, although that does not distort the estimation of the interaction odds ratio. In this study, the case-case analysis provides less infor-

mation than the kin-cohort analysis, but it uses independent data to assess interaction. Its results support the findings given by the kin-cohort approach.

Findings from several other studies of mutation carriers lend support to the findings of this investigation. Jernstrom *et al.*³ recently found no difference in age at first birth between 248 BRCA1/2 mutation carriers diagnosed with breast cancer at or before age 40 and matched carrier controls drawn from genetic-counseling centers in North America. In an earlier publication that may have included some of

the same cases, Narod *et al.*⁵ found no effect of age at first birth on breast cancer incidence but did find that higher parity and later age at last birth were linked to higher incidence. Within a group of 46 German BRCA1 mutation carriers, Chang-Claude *et al.*⁴ reported no difference in breast cancer risk between women giving birth before or after age 25.

Indirect evidence comes from analyses of women who were not tested for mutations but who were at substantial familial risk. In an early case series of hereditary breast cancer,¹⁶ a large cohort of nurses,¹⁷ and a large case-control study in Wisconsin and New England,¹⁸ earlier birth was not a protective factor in women with family history of breast cancer. In the case-control study used to fit the Gail model,¹⁹ early birth was less protective in women with family history of cancer; subsequent validation studies also showed this negative interaction between age at first birth and family history.^{20–22} This evidence, though consistent with our findings, is indirect because only a fraction of the women with substantial familial risk carry mutations in BRCA1/2.

If, as the present data suggest, a mutation carrier's age at her first birth has little effect on her breast cancer risk, is this part of a more general deviation in cancer risk factors? No clear pattern has emerged in the reports to date. Grabrick *et al.*²⁴ recently reported that oral contraceptive use was associated with increased breast cancer risk in women with strong family history. Ursin²⁶ reported greatly increased risk associated with 4 years or more of oral contraception in a small series of young Ashkenazi Jewish breast cancer patients. Rebbeck *et al.*²⁵ reported reduced risk in BRCA1 carriers after oophorectomy, the pattern seen in the general population. In the small German study,⁴ older age at menarche did show the typical relation to breast cancer risk. Johansson *et al.*²³ noted a higher risk of breast cancer diagnosed within a year of giving birth among Swedish carriers of BRCA1 mutations compared with noncarriers, with an intermediate level of risk in BRCA2 mutation carriers.

We have no simple explanation of why lower breast cancer risk would not follow earlier first birth in BRCA1/2 mutation carriers. In general, age at first birth and parity serve as simple indicators of a more complex set of influences of reproductive history. Indeed, pregnancy appears to have multiple subtle effects on breast cancer risk in the general population, increasing risk immediately after a pregnancy and then reducing it.^{1,2} Pregnancy probably produces these countervailing effects because the estrogen surge promotes nascent breast cancer whereas the differentiation of ductal tissue seen in late pregnancy reduces the number of cell cycles and attendant errors in replication. In most women, the balance of these effects yields reduction in long-term risk with earlier first term, or near-term, pregnancy. In carriers of BRCA1 or BRCA2 mutations, it appears that the balance may be different. Until there are more epidemiologic data on risks in carriers and more fundamental understanding of either the genes or the effect of first birth, it is premature to assume that the predictors of breast cancer risk will apply to the women carrying a mutation in one of the genes that predisposes to high risk of cancer.

Acknowledgments

We thank Mary McAdams, IMS, Inc., for expert statistical computing, and Katrina Wahl for manuscript preparation.

Appendix

Kin-Cohort Models for Effect of Age at First Birth

To model the effect of the age at first birth on the age-specific breast cancer risk of BRCA1/BRCA2 mutation carriers and noncarriers, we used the Cox proportional hazard model with baseline hazard function being stratified by the carrier status. Thus, if T denotes the age at onset of the disease, G denotes the mutation status, X denotes the environmental exposure, and Z denotes possible confounders, we considered the following model for the hazard of the disease:

$$\Pr(T = t | T \geq t, G, X) = \lambda(t | G, X) \\ = \lambda_{0G}(t) \exp(\beta_G X + \gamma Z)$$

where, $\lambda_{0G}(t)$ denotes the baseline ($X=0, Z=0$) hazard for noncarriers ($G=0$) and carriers ($G=1$). In this model, $\beta_G, G=0,1$ measures the effect of the environmental risk factor X on the hazard for noncarriers and carriers, respectively. We assumed the baseline hazard functions to be piece wise constant in the intervals $<35, 35-45, 45-55, 55-65, 65-75, >75$ for both noncarriers and carriers with two different sets of hazard parameters for the two groups. In the kin-cohort analysis, we estimated the parameters of the above model from the

likelihood¹⁰ of the relatives' disease incidence data, given their reproductive history and the volunteer's genotype data.

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