Prevalence and Predictors of *BRCA1* and *BRCA2* Mutations in a Population-Based Study of Breast Cancer in White and Black American Women Ages 35 to 64 Years

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Abstract

Although well studied in families at high-risk, the roles of mutations in the *BRCA1* and *BRCA2* genes are poorly understood in breast cancers in the general population, particularly in Black women and in age groups outside of the very young. We examined the prevalence and predictors of *BRCA1* and *BRCA2* mutations in 1,628 women with breast cancer and 674 women without breast cancer who participated in a multicenter population-based case-control study of Black and White women, 35 to 64 years of age. Among cases, 2.4% and 2.3% carried deleterious mutations in *BRCA1* and *BRCA2*, respectively. *BRCA1* mutations were significantly more common in White (2.9%) versus Black (1.4%) cases and in Jewish (10.2%) versus non-Jewish (2.0%) cases; *BRCA2* mutations were slightly more frequent in Black (2.6%) versus White (2.1%) cases. Numerous familial and demographic factors were significantly associated with *BRCA1* and, to a lesser extent, *BRCA2* carrier status, when examined individually. In models considering all predictors together, early onset ages in cases and in relatives, family history of ovarian cancer, and Jewish ancestry remained strongly and significantly predictive of *BRCA1* carrier status, whereas *BRCA2* predictors were fewer and more modest in magnitude. Both the combinations of predictors and effect sizes varied across racial/ethnic and age groups. These results provide first-time prevalence estimates for *BRCA1/BRCA2* in breast cancer cases among understudied racial and age groups and show key predictors of mutation carrier status for both White and Black women and women of a wide age spectrum with breast cancer in the general population. (Cancer Res 2006; 66(16): 8297-308)

Introduction

Germ line mutations in *BRCA1* and *BRCA2*, the two autosomal dominant breast cancer susceptibility genes, account for the majority of breast and ovarian cancers in families with high-risk profiles, with carriers having a 26% to 84% lifetime risk of breast cancer and a 10% to 50% lifetime risk of ovarian cancer (1–7). Most insights regarding the frequency of mutations in breast cancer cases have been derived from family-based and clinic-based studies of women with selected high-risk profiles. Few studies have assessed the frequency of mutations among women who reflect the wider spectrum of breast cancer in the general population, and all but one (5) of the population-based studies of both genes focused exclusively on young women (8–12). As a result, mutation frequency among women with breast cancer who were not young at diagnosis is unclear, although statistical models suggest that mutations are less common in older cases (9, 13). Because breast cancer incidence is highest in middle-aged and older women, clarifying the contribution of *BRCA1/BRCA2* mutations in these age groups through direct testing is an important public health priority. Of equal importance is the acquisition of information on mutation frequency in African-American women. Studies of any notable size have focused almost exclusively on White women, resulting in a paucity of information on minority women (14).

Within a population-based study of breast cancer in White and Black American women ages 35 to 64 years, we have examined the frequency of *BRCA1/BRCA2* mutations in cases and controls and the relative importance of personal characteristics and family history in predicting mutation status in cases.

Materials and Methods

Study population. This study was conducted within the National Institute of Child Health and Human Development's Women's Contraceptive and Reproductive Experiences (CARE) Study, details of which have been

Note: Supplementary data for this article are available at Cancer Research Online (http://cancerres.aacrjournals.org/).

The findings and conclusions in this report are those of the authors (R.J. Coates, P.A. Marchbanks, J.A. McDonald, and S. Folger) and do not necessarily represent the views of the Centers for Disease Control and Prevention.

R. Spirtas is retired.

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described elsewhere (15). Briefly, this population-based case-control study was conducted in five metropolitan areas of the U.S. (Atlanta, Detroit, Los Angeles, Philadelphia, and Seattle). Cases, ascertained by the Surveillance, Epidemiology, and End Results (SEER) population-based cancer registries at four sites and by field staff monitoring hospital records at the fifth site, were White and Black women 35 to 64 years of age with no previous breast cancer diagnosis who were diagnosed with invasive breast cancer from July 1994 to April 1998. Younger and Black cases were oversampled. Controls were women with no prior diagnosis of breast cancer who were ascertained using centralized random-digit dialing. Control selection fractions were designed to match expected frequencies of cases within strata of study center, race, and age group. Altogether, 4,575 cases (76.5% of those eligible) and 4,682 controls (78.6% of those eligible) completed an in-person interview on breast cancer risk factors including family history.

Available funding allowed the collection of blood from 33% of interviewed women. All cases and controls with a first-degree family history of breast cancer, plus a random sample of those without a first-degree family history (the latter was based on sampling fractions specific to case-control status, study center, race, and age) were asked to donate blood. Among 2,049 cases and 1,954 controls selected for blood collection, 1,644 (80.2%) cases and 1,451 (74.3%) controls provided blood. This represented 35.9% and 31.0% of all interviewed CARE cases and controls, respectively.

In both cases and controls targeted for blood draw, the proportions who gave blood did not vary by age. Those who gave blood were more apt to have local stage disease (63.5% versus 56.7%, $P = 0.03$), to be White (cases, 69.9% versus 42.0%, $P < 0.001$; controls, 68.6% versus 44.1%, $P < 0.001$), and to have attended college (cases, 59.9% versus 48.0%, $P < 0.001$; controls, 57.2% versus 47.1%, $P < 0.001$). Among controls (but not cases), those who gave blood were more likely to have a positive family history of breast cancer (52.8% versus 43.6%, $P = 0.001$). The weighting for sampling probabilities used in these analyses (described below) ameliorated these differences, to some extent, by allowing sampled women with the same combinations of sampling factors as women who refused to donate blood to represent their contributions.

All 1,644 blood samples from cases were included in the mutation scan. A subset of control samples was tested, specifically, all samples from controls with a first-degree family history of breast cancer plus a random sample of the remaining controls, or a total of 674 of the 1,451 control samples available. Of 1,644 case and 674 control samples tested, 1,625 and 672 yielded results for *BRCA1,* and 1,626 and 674 yielded results for *BRCA2,* respectively. All analyses accounted for the sampling structure used in selecting the study group.

Laboratory methods. Genomic DNA was purified from frozen buffy coats using a phenol-based extraction method. *BRCA1* and *BRCA2* were amplified by PCR in 36 and 47 amplicons, respectively. PCR, denaturing high-performance liquid chromatography (DHPLC), and sequencing methods are described in more detail in the Supplemental Methods. Primer sequences and PCR conditions are listed in Supplemental Table S1. Heteroduplex formation and DHPLC in 96-well plates were carried out as described by Eng et al. (16) using now-standard protocols (17), except that the number of *BRCA1* amplicons run at two DHPLC elution temperatures was reduced from 19 to 5 (Supplemental Table S1). Variants were detected by visual observation and double scoring of DHPLC elution profiles. Any samples that eluded two peaks, peaks with shoulders, or wide or shifted peaks were further examined by direct bidirectional sequencing. Bidirectional DNA sequencing was done on all variants occurring in 10% or less of samples using ABI Big Dye Terminator sequencing kits as described in the Supplemental Methods.

Although results were collected on all types of DNA variants, the analyses here focus solely on changes presumed to be disease associated, including all protein-truncating mutations, a small subset of missense changes known to be disease-associated (18, 19) such as those in the *BRCA1* RING finger motif, and splice site alterations within 2 bp of intron/exon boundaries. The only exception was the exclusion of a small subset of *BRCA2* protein truncating variants known to be common polymorphisms (20). A listing of all disease-associated changes observed in this study is provided in Supplemental Table S2.

Statistical methods. Sampling weights were computed by dividing the total number of women interviewed in each of 240 strata defined by case-control status, race (Black, White), age group (5-year groups), center, and first-degree family history of breast cancer (present, absent) by the number of women sampled for *BRCA1/BRCA2* genotyping. Essentially, a sampling weight equaled the number of women in the overall CARE Study population that a sampled woman "represented." For example, if half of the women in a stratum were sampled, the weight for each sampled woman would be 2, as each represented two women from the study. The lower the proportion sampled from a stratum is, the higher the sampling weight per sampled woman. These weights allowed results from tested samples to be adjusted so that they represented the proportions and effects expected if the entire CARE Study population had been tested, and were used to calculate weighted proportions and weighted odds ratios (OR).

To assess the prevalence of mutations in the CARE Study participants, weighted proportions of mutation carriers [with 95% confidence intervals (CI)] were calculated. The proportions and SEs for CIs were obtained using the Stata/SE 8.2 "svy" commands. Differences in proportions by strata were assessed using a Pearson χ^2 test.

To estimate the frequency of mutations in the general population, we assumed that the frequencies in tested cases were representative of all prevalent cases, and that the frequencies in tested controls were representative of women without breast cancer in the general population. This assumption allowed us to apply the mutation frequencies in tested cases and controls to the proportions of the general population who did and did not have a history of breast cancer, which we determined using a breast cancer prevalence estimate from SEER data.[13] To estimate population mutation frequencies, the weighting needed to account for both the previously described within-study sampling of blood specimens and the sampled nature of the CARE Study itself. For cases, we used weights that corresponded with the total number of incident cases over the study period. For controls, the weights were set to correspond with the number of eligible women in the sampling strata according to the U.S. Bureau of Census annual estimates of the population that were averaged over the study years and adjusted for study eligibility criteria (phone ownership, no prior breast cancer). These case and control weighted estimates were then applied to the appropriate percentages of the population (based on prevalence estimates) and cumulated to estimate the frequency of mutations in the general population of Black and White women ages 35 to 64 years in the five Women's CARE Study sites.

To evaluate the relative predictive importance of demographic and family history characteristics, a case-only analysis assessing the odds of having a mutation in relation to these factors was done. Polytomous logistic regression models assessing associations of demographic and familial factors with the odds of carrying a mutation in *BRCA1* or *BRCA2* were used to estimate ORs and 95% CIs. "Univariate" ORs for the individual associations of family history and demographic factors with mutation carrier status were computed among all cases, adjusted only for sampling weights and study matching factors (age, race, and study site). Multivariate analyses examined family history and demographic factors in combined models that simultaneously considered the effects of these potential predictors and accounted for matching factors and sampling weights. The collinearity of familial factors, in that all of these variables would be compared against a common reference group (no family history), precluded simultaneous assessment of all familial factors among all cases (with or without family history) in combined models (21). Thus, two sets of models were generated. Model I assessed the odds of being a carrier among all cases (with and without family history) in relation to demographic features and the presence or absence of any family history of breast cancer or ovarian cancer. Model II, confined to cases with a first- or second-degree family history of breast cancer, examined more detailed family history variables.

[13] SEER Cancer Statistics Review (1975-2002) http://seer.cancer.gov/csr/1975_2002/[updated 2005; cited 5 A.D. Nov 5]. Available from: http://seer.cancer.gov/csr/1975_2002/.

The study protocol was approved by institutional review boards at each site. Written informed consent was obtained from all participants for the interview and for the use of specimens for research laboratory analysis.

Results

The 1,628 breast cancer cases and 674 controls included in this study were similar with regard to age (case and control mean ages, 49.3 and 49.5) and race (Table 1). Because sampling maximized inclusion of women with a first-degree family history of breast cancer, the proportions with family history exceeded those in the underlying CARE Study. All subsequent analyses (Tables 2–5) accounted for sampling through sample weight adjustment.

Table 1. Distribution of demographic and family history characteristics in cases and controls

	Cases (*N* = 1,628)	Controls (*N* = 674)
	n (%)	*n* (%)
Demographics		
Age (years) at reference*		
<45	548 (33.7)	221 (32.8)
45+	1,080 (66.3)	453 (67.2)
Mean age	49.3 (SD 8.6)	49.5 (SD 8.6)
Race*		
White	1,145 (70.3)	461 (68.4)
Black	483 (29.7)	213 (31.6)
Religion reported as Jewish		
No	1,542 (94.7)	659 (97.8)
Yes	86 (5.3)	15 (2.2)
Personal history of bilateral breast cancer		
No	1,581 (97.1)	—
Yes	47 (2.9)	—
Family history of breast cancer*		
None	429 (26.4)	224 (33.2)
Any first or second degree	860 (52.8)	276 (40.9)
First degree	613 (37.7)	172 (25.5)
Second degree only	247 (15.2)	104 (15.4)
No first degree, unknown second	297 (18.2)	159 (23.6)
Adopted or unknown first degree	42 (2.6)	15 (2.2)
Number of relatives with breast cancer*		
One	596 (36.6)	203 (30.1)
Two	167 (10.3)	64 (9.5)
Three or more	97 (6.0)	9 (1.3)
Breast cancer in one or more relatives diagnosed before age 45*		
Yes	201 (12.3)	53 (7.9)
All diagnosed age 45+	608 (37.3)	206 (30.6)
Family history of bilateral breast cancer*		
Unilateral only	669 (51.9)	222 (44.4)
Bilateral	191 (14.8)	54 (10.8)
Family history of ovarian cancer		
None	877 (53.9)	364 (54.0)
Any first or second degree	82 (5.0)	32 (4.7)
First degree	37 (2.3)	15 (2.2)
Second degree only	45 (2.8)	17 (2.5)
No first degree, unknown second	599 (36.8)	254 (37.7)
Adopted or unknown first degree	70 (4.3)	24 (3.6)

NOTE: Proportions in this table reflect the oversampling of younger cases, Black cases, and women with a family history of breast cancer.
*Cases and controls were sampled according to race, age, center, and family history of breast cancer.

Frequency of mutations by demographic and familial characteristics. *BRCA1* mutations were found in 2.4% of cases and 0.04% of controls, and *BRCA2* mutations in 2.3% and 0.4% of controls (Table 2). Among cases, the prevalence of *BRCA1* mutations decreased with increasing age ($P < 0.001$), was twice as frequent in White (2.9%) compared with Black cases (1.4%, $P < .05$), and was substantially more common in cases of Jewish ancestry (10.2%, $P < .001$). In cases, *BRCA1* mutation frequency varied with family history; 1.9% in cases with no family history of breast cancer, 3.1% of cases with only a second-degree family history, and 5.6% of cases with first-degree family history carried *BRCA1* mutations ($P = 0.015$). *BRCA1* mutations were significantly more frequent in cases when the following characteristics were present: a relative diagnosed before age 45 (12.8%, $P < .001$), a relative with bilateral breast cancer (8%, $P < .001$), three or more affected relatives (8.7%, $P < 0.002$), a family history of ovarian cancer (14.1%, $P < 0.001$), and a family history of breast and ovarian cancer (27.3%, $P < 0.001$). The one control with a *BRCA1* mutation had a family history of breast but not ovarian cancer.

BRCA2 mutation frequency was greater in cases with a younger diagnosis age, with 4.0% of cases ages 35 to 44, and 1.5% of cases ages 45 to 64 ($P = 0.003$) carrying a *BRCA2* mutation. *BRCA2* prevalence was slightly higher in Black (2.6%) versus White (2.1%) cases and was more frequent in non-Jewish (2.3%) versus Jewish (1.1%) cases but these differences were not statistically significant. *BRCA2* mutation frequency was similar in cases with no family history of breast cancer (2.0%) and only second-degree family history (1.9%) but was marginally higher in cases with a first-degree family history (5.0%, $P = 0.06$). Compared with cases with no family history, a higher proportion of *BRCA2* mutations was found in cases with three or more relatives with breast cancer (10.7%, $P = 0.004$) and in cases with a relative with breast cancer before 45 years of age (7.4%, $P = 0.002$). *BRCA2* mutations were more common in cases with a family history of both breast and ovarian cancer than in cases without a family history of either disease, but this result was of borderline significance ($P = 0.054$). *BRCA2* mutations were found in five control samples (0.4%), four of whom had a first-degree family history of breast cancer.

Mutation frequency by family history according to age, race, and Jewish ancestry. Among cases in both age groups (35-44 and 45-64 years), *BRCA1* mutation prevalence was greater in those with a relative with early breast cancer onset (ages 35-44, 26.8%, $P < 0.001$; 45-64, 4.0%, $P = 0.022$) and a family history of ovarian cancer (ages 35-44, 28.5%, $P < 0.001$; 45-64, 4.5%, $P = 0.038$; Table 3). In cases 35 to 44 years of age but not discernibly in cases ages 45 to 64 years of age, *BRCA1* mutation prevalence was higher in those with first-degree family history of breast cancer (15.0%, $P = 0.003$), multiple affected relatives ($P < 0.001$), and a family history of bilateral breast cancer ($P < 0.001$). Among cases 35 to 44 years of age, *BRCA2* mutation prevalence was significantly greater in cases with early onset breast cancer in a relative ($P = 0.001$), three or more affected relatives ($P < 0.001$), and family history of bilateral breast cancer ($P = 0.023$). Although *BRCA2* mutations were more common among cases 45 to 64 years of age with versus without the above family history features, these differences were not statistically significant.

Table 2. Weighted distribution of *BRCA1* and *BRCA2* mutations by demographics and family history in cases and controls

	BRCA1						*BRCA2*					
	Cases			Controls			Cases			Controls		
	n (%)*	95% CI*	*P* †	*n* (%)*	95% CI*	*P* †	*n* (%)*	95% CI*	*P* †	*n* (%)*	95% CI*	*P* †
Overall	52 (2.4)	1.7-3.1	—	1 (0.04)	0.0-0.1	—	44 (2.3)	1.5-3.0	—	5 (0.4)	0.0-0.8	—
Age at reference date												
35-44	40 (6.3)	4.2-8.4		1 (0.1)	0.0-0.4		23 (4.0)	2.1-6.0		1 (0.1)	0.0-0.4	
45-64	12 (0.7)	0.2-1.1	<0.001	0 (0.0)	—	0.145	21 (1.5)	0.7-2.2	0.003	4 (0.5)	0.0-1.2	0.221
35-39	26 (8.2)	5.0-11.4		0 (0.0)			10 (3.6)	1.3-5.9		0 (0.0)	—	
40-44	14 (4.5)	1.8-7.3		1 (0.2)	0.0-0.7		13 (4.4)	1.4-7.5		1 (0.2)	0.0-0.7	
45-49	5 (0.7)	0.1-1.4		0 (0.0)	—		5 (1.3)	0.0-2.8		1 (1.1)	0.0-3.3	
50-54	2 (0.3)	0.0-0.8		0 (0.0)	—		4 (1.1)	0.0-2.4		1 (0.2)	0.0-0.7	
55-59	1 (0.3)	0.0-0.8		0 (0.0)	—		6 (1.5)	0.1-2.8		1 (0.3)	0.0-0.9	
60-64	4 (1.5)	0.0-3.1	<0.001	0 (0.0)	—	0.918	6 (2.1)	0.2-3.9	0.079	1 (0.4)	0.0-1.1	0.504
Religion reported as Jewish												
No	42 (2.0)	1.4-2.7		1 (0.04)	0.0-0.1		42 (2.3)	1.5-3.1		4 (0.4)	0.0-0.8	
Yes	10 (10.2)	3.1-17.3	<0.001	0 (0.0)	—	0.891	2 (1.1)	0.0-2.7	0.318	1 (2.2)	0.0-6.5	0.091
Race												
Black	10 (1.4)	0.5-2.4		0 (0.0)	—		16 (2.6)	1.1-4.1		3 (0.9)	0.0-2.1	
White	42 (2.9)	2.0-3.9	0.049	1 (0.1)	0.0-0.2	0.468	28 (2.1)	1.2-3.0	0.593	2 (0.1)	0.0-0.3	0.026
Non-Jewish	32 (2.4)	1.5-3.3		1 (0.1)	0.0-0.2		26 (2.2)	1.2-3.1		1 (0.1)	0.0-0.2	
Jewish	10 (10.2)	3.1-17.3	<0.001	0 (0.0)	—	0.872	2 (1.1)	0.0-2.7	0.374	1 (2.4)	0.0-7.2	<0.001
Personal history of bilateral breast cancer												
No	50 (2.4)	1.7-3.1		not applicable			42 (2.3)	1.5-3.1		not applicable		
Yes	2 (2.8)	0.0-6.7	0.846				2 (2.5)	0.0-6.1	0.878			
Family history of breast cancer												
None	10 (1.9)	0.7-3.1		0 (0.0)	—		8 (2.0)	0.6-3.5		1 (0.5)	0.0-1.5	
First or second degree	39 (4.3)	2.8-5.7	0.023	1 (0.2)	0.0-0.5	0.226	32 (3.3)	2.0-4.6	0.241	4 (0.7)	0.0-1.4	0.760
First degree	30 (5.6)	3.5-7.7		1 (0.5)	0.0-1.4		28 (5.0)	3.1-6.8		4 (2.0)	0.0-4.1	
Second degree only	9 (3.1)	1.0-5.2	0.015	0 (0.0)	—	0.303	4 (1.9)	0.0-3.7	0.060	0 (0.0)	—	0.173
Number of relatives with breast cancer												
One	20 (3.1)	1.6-4.6		0 (0.0)	—		16 (2.5)	1.1-4.0		3 (0.7)	0.0-1.5	
Two	13 (7.4)	2.9-11.8		1 (0.6)	0.0-1.9		6 (3.2)	0.3-6.1		0 (0.0)	—	
Three or more	6 (8.7)	1.0-16.4	0.002	0 (0.0)	—	0.250	10 (10.7)	4.2-17.3	0.004	1 (10.1)	0.0-29.1	0.048
Breast cancer before age 45 in a relative												
Yes	24 (12.8)	7.3-18.3		1 (0.8)	0.0-2.4		13 (7.4)	2.8-12.0		2 (1.8)	0.0-4.5	
All diagnosed age 45+	15 (2.4)	1.1-3.7	<0.001	0 (0.0)	—	0.106	16 (1.8)	0.9-2.7	0.002	2 (0.5)	0.0-1.2	0.408
Family history of bilateral breast cancer												
Unilateral only	23 (3.2)	1.7-4.6		1 (0.2)	0.0-0.6		24 (2.9)	1.6-4.2		4 (0.9)	0.0-1.7	
Bilateral	16 (8.0)	3.8-12.3	<0.001	0 (0.0)	—	0.567	8 (4.8)	1.0-8.6	0.241	0 (0.0)	—	0.707
Family history of ovarian cancer												
None	28 (2.4)	1.4-3.3		1 (0.1)	0.0-0.2		21 (2.1)	1.1-3.1		3 (0.6)	0.0-1.3	
First or second degree	13 (14.1)	6.1-22.0	<0.001	0 (0.0)	—	0.773	3 (4.0)	0.0-9.2	0.358	0 (0.0)	—	0.686
Family history of breast and ovarian cancer												
No breast, no ovarian	8 (1.5)	0.4-2.6		0 (0.0)	—		8 (2.1)	0.6-3.6		1 (0.5)	0.0-1.6	
Yes breast, no ovarian	20 (3.7)	1.9-5.5		1 (0.3)	0.0-0.8		13 (2.1)	0.9-3.3		2 (0.6)	0.0-1.4	
No breast, yes ovarian	2 (10.7)	0.0-24.9		0 (0.0)	—		0 (0.0)	—		0 (0.0)	—	
Yes breast, yes ovarian	11 (27.3)	12.2-42.4	<0.001	0 (0.0)	—	0.769	3 (11.3)	0.0-25.3	0.054	0 (0.0)	—	0.969

NOTE: Mutation frequencies for each gene are examined in comparison with cases and controls that tested negative for mutations in that gene. Cases and controls that tested positive for the other gene have been excluded.

*Proportions and CIs weighted for the age, race, center, and first-degree family history sampling probabilities.

† *P* value from Pearson χ^2 test compares proportions within cases and within controls by demographic factors and by family history features.

In both White and Black cases, *BRCA1* mutation frequency was significantly greater among cases ages 35 to 44, those with a relative with early onset breast cancer and those with multiple affected relatives (Table 3). *BRCA1* mutation prevalence was significantly elevated in White cases with family histories of bilateral cancer and of ovarian cancer; results were similar but statistically nonsignificant in Black cases. *BRCA2* mutation frequency was significantly elevated in White cases with a relative

Table 3. Weighted distribution of *BRCA1* and *BRCA2* mutations in cases by family history (and by age in the racial and Jewish ancestry groups) according to age, race, and Jewish ancestry

	BRCA1			*BRCA2*			*BRCA1*			*BRCA2*		
	n (%)*	95% CI*	*P* †	*n* (%)*	95% CI*	*P* †	*n* (%)*	95% CI*	*P* †	*n* (%)*	95% CI*	*P* †
	AGE 35-44 YEARS						AGE 45-64 YEARS					
Family history of breast cancer												
None	8 (3.6)	1.1-6.1		4 (2.8)	0.0-5.7		2 (0.9)	0.0-2.1		4 (1.6)	0.0-3.1	
First degree	20 (15.0)	8.4-21.5		14 (10.0)	4.9-15.1		10 (2.3)	0.9-3.8		14 (3.3)	1.5-5.1	
Second degree only	9 (8.2)	2.9-13.5	0.003	2 (2.6)	0.0-6.3	0.055	0 (0.0)	—	0.076	2 (1.5)	0.0-3.5	0.359
Breast cancer in first or second degree relative before age 45												
Yes	18 (26.8)	14.6-39.0		9 (16.3)	4.9-27.6		6 (4.0)	0.7-7.3		4 (2.4)	0.0-4.8	
All diagnosed age 45+	11 (6.5)	2.4-10.5	<0.001	7 (2.6)	0.6-4.5	0.001	4 (0.6)	0.0-1.2	0.022	9 (1.4)	0.5-2.4	0.750
Number of relatives with breast cancer												
One	15 (7.6)	3.5-11.6		5 (2.8)	0.0-5.6		5 (0.8)	0.1-1.6		11 (2.4)	0.7-4.1	
Two	9 (18.5)	6.0-31.1		5 (10.2)	0.5-19.8		4 (2.6)	0.0-5.3		1 (0.5)	0.0-1.6	
Three or more	5 (33.3)	8.3-58.3	<0.001	6 (29.1)	9.5-48.7	<0.001	1 (1.1)	0.0-3.3	0.393	4 (5.7)	0.0-11.3	0.167
Family history of bilateral breast cancer												
Unilateral only	16 (7.6)	3.5-11.7		10 (3.4)	1.2-5.5		7 (1.1)	0.3-1.9		14 (2.7)	1.0-4.3	
Bilateral	13 (21.6)	9.8-33.4	<0.001	6 (12.7)	1.5-24.0	0.023	3 (1.5)	0.0-3.2	0.797	2 (1.4)	0.0-3.3	0.503
Family history of ovarian cancer												
None	20 (4.9)	2.6-7.2		13 (3.4)	1.2-5.5		8 (0.9)	0.1-1.6		8 (1.4)	0.3-2.4	
First or second degree	11 (28.5)	12.4-44.7	<0.001	2 (4.6)	0.0-11.0	0.698	2 (4.5)	0.0-11.1	0.038	1 (3.7)	0.0-10.9	0.329
	WHITE						BLACK					
Family history of breast cancer												
None	7 (2.1)	0.5-3.7		5 (1.8)	0.2-3.4		3 (1.5)	0.0-3.2		3 (2.4)	0.0-5.4	
First degree	24 (5.9)	3.5-8.2		18 (4.3)	2.3-6.3		6 (5.1)	0.6-9.6		10 (6.5)	2.4-10.5	
Second degree only	8 (3.6)	1.1-6.2	0.063	3 (2.0)	0.0-4.2	0.227	1 (1.4)	0.0-4.3	0.180	1 (1.5)	0.0-4.3	0.188
Breast cancer in first or second degree relative before age 45												
Yes	19 (14.7)	7.7-21.7		8 (7.0)	1.2-12.7		5 (9.0)	0.4-17.7		5 (8.2)	0.7-15.7	
All diagnosed age 45+	13 (2.6)	1.1-4.2	<0.001	11 (1.5)	0.6-2.5	0.011	2 (1.7)	0.0-4.2	0.014	5 (2.6)	0.2-4.9	0.154
Number relatives with breast cancer												
One	17 (3.6)	1.7-5.4		12 (2.8)	0.9-4.7		3 (1.8)	0.0-4.1		4 (1.7)	0.0-3.4	
Two	11 (8.2)	2.7-13.6		4 (2.2)	0.0-4.4		2 (4.8)	0.0-11.6		2 (5.9)	0.0-14.9	
Three or more	4 (6.6)	0.0-13.4	0.023	5 (6.7)	0.9-12.5	0.230	2 (13.7)	0.0-34.1	0.021	5 (19.8)	2.9-36.8	0.002
Family history of bilateral breast cancer												
Unilateral only	19 (3.5)	1.7-5.3		17 (2.9)	1.3-4.4		4 (2.2)	0.0-4.5		7 (2.9)	0.7-5.2	
Bilateral	13 (8.4)	3.5-13.2	0.008	4 (3.6)	0.0-7.9	0.557	3 (7.1)	0.0-16.0	0.115	4 (7.8)	0.0-15.8	0.247
Family history of ovarian cancer												
None	23 (2.6)	1.4-3.8		14 (1.7)	0.7-2.8		5 (1.7)	0.2-3.2		7 (2.9)	0.4-5.4	
First or second degree	12 (17.7)	7.3-28.0	<0.001	3 (5.8)	0.0-13.3	0.084	1 (5.5)	0.0-15.9	0.258	0 (0.0)	—	0.517
Age at diagnosis												
35-44 years	32 (7.5)	4.7-10.3		15 (3.5)	1.5-5.6		8 (3.9)	1.0-6.8		8 (4.9)	0.9-8.9	
45-64 years	10 (0.9)	0.2-1.6	<0.001	13 (1.5)	0.5-2.4	0.039	2 (0.3)	0.0-0.7	<0.001	8 (1.5)	0.3-2.7	0.032
	JEWISH (WHITES)						NON-JEWISH (WHITES)					
Family history of breast cancer												
None	2 (9.7)	0.0-23.3		0 (0.0)	—		5 (1.5)	0.2-2.8		5 (1.9)	0.2-3.6	
First degree	6 (15.5)	4.0-27.0		2 (5.2)	0.0-12.3		18 (5.0)	2.7-7.2		16 (4.2)	2.2-6.3	
Second degree only	1 (9.0)	0.0-25.9	0.796	0 (0.0)	—	0.337	7 (3.3)	0.8-5.8	0.067	3 (2.1)	0.0-4.5	0.314
Breast cancer in first or second degree relative before age 45												
Yes	5 (43.4)	15.1-71.7		0 (0.0)	—		14 (12.7)	5.6-19.9		8 (7.2)	1.2-13.2	
All diagnosed age 45+	2 (6.4)	0.0-15.9	0.042	2 (3.2)	0.0-7.7	0.401	11 (2.3)	0.8-3.8	<0.001	9 (1.4)	0.5-2.4	0.009

(*Continued on the following page*)

Table 3. Weighted distribution of *BRCA1* and *BRCA2* mutations in cases by family history (and by age in the racial and Jewish ancestry groups) according to age, race, and Jewish ancestry (Cont'd)

	BRCA1			*BRCA2*			*BRCA1*			*BRCA2*		
	n (%)*	95% CI*	*P* †	*n* (%)*	95% CI*	*P* †	*n* (%)*	95% CI*	*P* †	*n* (%)*	95% CI*	*P* †
	JEWISH (WHITES)						NON-JEWISH (WHITES)					
Number relatives with breast cancer												
One	3 (10.0)	0.0-22.5		2 (4.2)	0.0-10.1		14 (3.2)	1.4-5.0		10 (2.7)	0.8-4.7	
Two	3 (19.8)	0.0-42.1		0 (0.0)	—		8 (7.0)	1.5-12.6		4 (2.4)	0.0-4.8	
Three or more	1 (13.6)	0.0-38.4	0.832	0 (0.0)	—	0.548	3 (5.8)	0.0-12.7	0.032	5 (7.4)	1.0-13.8	0.222
Family history of bilateral breast cancer												
Unilateral only	4 (10.0)	0.0-20.6		2 (3.4)	0.0-8.1		15 (3.0)	1.3-4.8		15 (2.8)	1.2-4.5	
Bilateral	3 (25.0)	0.0-52.0	0.518	0 (0.0)	—	0.475	10 (7.4)	2.5-12.3	0.008	4 (3.8)	0.0-8.2	0.611
Family history of ovarian cancer												
None	7 (12.3)	2.3-22.2		1 (1.0)	0.0-2.9		16 (1.9)	0.9-2.9		13 (1.8)	0.7-2.9	
First or second degree	1 (17.6)	0.0-54.1	0.757	0 (0.0)	—	0.853	11 (17.7)	7.0-28.3	<0.001	3 (6.1)	0.0-13.9	0.081
Age at diagnosis												
35-44 years	8 (26.6)	8.2-45.1		1 (2.4)	0.0-7.3		24 (6.2)	3.6-8.9		14 (3.6)	1.4-5.7	
45-64 years	2 (3.9)	0.0-10.1	0.010	1 (0.7)	0.0-2.2	0.376	8 (0.7)	0.1-1.2	<0.001	12 (1.5)	0.5-2.5	0.051

*Proportions and CI weighted for the age, race, center, and first-degree family history sampling probabilities.
†*P* value from Pearson χ^2 test compares proportions (in case) within strata of age, race, and Jewish ancestry by family history and by age.

with breast cancer before age 45 and in Black cases with multiple relatives with breast cancer.

Among Jewish cases, *BRCA1* mutations were more common in those with a first-degree family history of breast cancer, multiple affected relatives, and a family history of ovarian cancer, but results relied on small numbers and were not significant (Table 3). Jewish cases with a relative with breast cancer before age 45 had a greater proportion of *BRCA1* mutations (43.4%, $P = 0.042$) than those whose relatives were all age 45 or older at diagnosis (6.4%). *BRCA1* mutations were significantly more common in Jewish cases diagnosed before 45 years of age. The few *BRCA2* mutations observed limited analyses.

Multivariate results. When considered individually (univariate model adjusted only for matching factors and sampling weights), early onset age, Jewish ancestry, family history of ovarian cancer, first-degree family history of breast cancer, early onset in a relative, multiple affected relatives, and bilateral breast cancer in a relative were all significantly associated with *BRCA1* carrier status (Table 4). Among all cases (those with and without family history, model I), the multivariate logistic regression analyses found markedly elevated ORs for *BRCA1* mutation in cases who were diagnosed at ages 35 to 44 years, those with a family history of ovarian cancer, and those with Jewish ancestry (ORs, 9.5, 9.3, and 7.8, respectively). Early diagnosis age in cases remained highly predictive of *BRCA1* status across every subgroup (ORs ranging from 8 to 24). First-degree family history of breast cancer remained a significant but more modest predictor of the presence of a *BRCA1* mutation, overall and in White cases, as well as among both younger and older cases (ORs ranging from 3.5 to 4.0). In model II analyses (which were restricted to cases with a family history of breast cancer and incorporated detailed family history variables), four factors, diagnosis at ages 35 to 44 years in the case, Jewish ancestry, family history of ovarian cancer, and breast cancer in a relative before age 45 were all strongly related with *BRCA1* carrier status (ORs ranging from 4 to 9). Associations were comparable in White, Black and Jewish cases, although estimates were generally higher in the latter two groups. Overall and in all subgroups except Black cases, breast cancer in a first-degree relative was no longer significantly related to *BRCA1* mutation carriership in model II multivariate analyses. Although associated with increased odds of *BRCA1* mutation carriership individually, neither multiple affected relatives nor bilateral breast cancer in a relative retained significance in multivariate analyses.

In univariate analyses, early onset in cases, first-degree family history of breast cancer, family history of ovarian cancer, early onset of breast cancer in a relative, and multiple affected relatives were all significantly associated with increased odds of carrying a *BRCA2* mutation (Table 4). In multivariate analyses involving all cases (model I), the only factor that remained significant was early age of diagnosis in the case (overall OR, 2.8), which was also significant in Black (OR, 3.7) but not White cases. Multivariate model II analyses found only two factors, early diagnosis age in the case (OR, 2.5) and early diagnosis in a relative (OR, 2.3), to be associated with a significantly increased odds of being a *BRCA2* carrier. In Black cases with a family history of breast cancer, multivariate analyses found the presence of multiple relatives with breast cancer to be the only significant predictor of *BRCA2* status (OR, 5.0). In White cases with a family history of breast cancer, a family history of ovarian cancer (OR, 7.2) and a relative with early onset breast cancer (OR, 2.6) were both predictors of carrying a *BRCA2* mutation.

Table 5 provides the results of multivariate analyses of the odds of carrying a mutation in either gene. As expected, the risk estimates generally are intermediate of the separate results for *BRCA1* and *BRCA2* (Table 4).

Discussion

Although we collected data on all types of DNA variants including missense changes, we focus this report exclusively on

variants that cause a protein-truncating event, interrupt a splice site, or disrupt a well-recognized domain within the protein, such as the RING finger or BRCT domains, and are clearly highly likely to be disease-associated. In this study of women ages 35 to 64 years, we found very similar proportions of *BRCA1* and *BRCA2* mutations in cases, 2.4% and 2.3%, respectively. Mutations were much less frequent in controls (0.04% and 0.4%). Overall, we found that 4.6% of cases and 0.4% of controls had either a *BRCA1* or *BRCA2* mutation.

Mutation prevalence in the general population. The advantages of this study include its large sample size, inclusion of understudied groups of women, and direct mutation scanning in population controls. No other large population-based studies have directly tested controls, but several extrapolated population carrier prevalence from genotyped cases. Whittemore et al. estimated *BRCA1* mutation prevalence in the U.S. from a series of 525 breast cancer and 290 ovarian cancer cases as 0.24% in non-Hispanic non-Ashkenazi Whites and 1.2% in Ashkenazi Jewish Whites (22). The Anglian Breast Cancer Study of 1,220 cases estimated population prevalence as 0.07% to 0.09% for *BRCA1* and 0.14% to 0.22% for *BRCA2* (5), whereas Peto et al. estimated prevalence as 0.11% and 0.12% from a study of 617 cases (9). After accounting for the within-study sampling for blood collection, the sampled nature of the CARE Study itself, and the proportion of the general population with prevalent breast cancer, we estimate that among the aggregate of White and Black women ages 35 to 64 in the U.S., the population prevalence of *BRCA1* mutations is 0.06% and the prevalence of *BRCA2* mutations is 0.4%. These findings are compatible with earlier estimates, although our *BRCA1* frequency is lower and *BRCA2* frequency higher. Because earlier studies were confined largely to Whites, and because in the CARE Study, White women more often than Black women carried *BRCA1* mutations and Black women more often than White women carried *BRCA2* mutations, differences may reflect variations in racial distributions.

Mutation prevalence in cases. In our study, mutation frequency was higher in the youngest cases (35-44 years), with 6.3% and 4.0%, respectively, carrying *BRCA1* and *BRCA2* mutations. These proportions, particularly for *BRCA2*, exceed those in similar age groups in earlier population-based studies (5, 9, 11). Most insights regarding *BRCA1/BRCA2* in older breast cancer cases have come from statistical projections (9, 13, 23). The only previous large population-based study to directly assess both genes and include cases over age 45 years, the Anglian Study, observed a decreased mutation frequency with increasing age, with 0.3% *BRCA1* and 1.0% *BRCA2* carriers in cases 45 to 54 years of age (5). Two other large population-based studies included cases over age 45 years but assessed *BRCA1* alone; both found that mutation prevalence decreased with increasing age (22, 24). For the first time, the present study provides mutation scan data in a population-based setting on both genes in women diagnosed with breast cancer up to age 64. *BRCA1* mutation frequency decreased fairly steadily with age; *BRCA2* mutation frequency also decreased with age, although less dramatically. The slightly lower proportion overall and the broader dispersion of *BRCA2* mutations by age reported here further supports the older onset age (3, 5, 25) and lower penetrance that has been suggested for *BRCA2* (7, 26, 27). Additional weighting for the sampling from the underlying populations from which CARE cases were drawn had little effect on our estimates of prevalence in cases (from 2.4% to 2.2% for *BRCA1* and from 2.3% to 2.5% for *BRCA2*; results not shown). Mutation frequencies slightly exceed those in earlier studies, likely because of advances in mutation detection technology and population differences. Our sampling plan is an unlikely explanation for the observed differences because sampling was accounted for through weighting of the statistical analyses.

BRCA1/BRCA2 mutation prevalence estimates in the cases presented here are much lower than those observed in clinic-based studies (28–30), in which mutation prevalence ranges from as high as 20% to 55%. This contrast is not surprising given that the clinic-based studies have concentrated on women perceived to be at higher risk of carriership, such as those with large numbers of affected individuals or those with a family history of both breast and ovarian cancer.

Predictors of carrier status. Numerous factors were individually associated with the presence of a mutation in cases, including early onset and many components of family history. Although several of these factors have been previously shown to occur more frequently in *BRCA1/BRCA2* mutation carriers (5, 9–11), most prior work focused on younger, White women, and/or women at high risk, leaving this study unique in its assessment of these factors in understudied segments of the general population. A few previous studies used a multivariate approach to evaluate potential predictors of carriership, but with the exception of one ethnically diverse study of families at high risk (31), they focused on selected women at high-risk, typically of European or Ashkenazi ancestry (1, 28, 32–36). We used two sets of multivariate models, one including all cases and the other for those with a family history of breast cancer. Among all cases, early onset (ages 35-44) in cases, Jewish ancestry, ovarian cancer family history, and first-degree family history of breast cancer were significant predictors of *BRCA1* mutation status. Among cases with a family history of breast cancer, early onset in a case, family history of ovarian cancer, Jewish ancestry, and early onset in a relative each remained as powerful, independent predictors of *BRCA1* carrier status in multivariate analyses, whereas results for family history of bilateral breast cancer and multiple affected relatives were no longer statistically significant. Multivariate models for *BRCA2* yielded fewer significant predictors and the magnitude of effects were much lower than for *BRCA1*. Among all cases, only one factor, early age of diagnosis in the case, was a significant predictor of *BRCA2* status; this association was relatively modest and remained statistically significant in only one subgroup, Black cases. Among cases with a family history, only two factors, early onset in the case and early onset in a relative, were significantly predictive of *BRCA2* status.

Findings by race and Jewish ancestry. There has been a paucity of research on *BRCA1/BRCA2* in Black women and most studies have focused on clinic populations at high risk (14, 31, 37–42). In one of the only population-based studies to include Black women, no protein-truncating *BRCA1* mutations were found in 88 cases and 79 controls (43). In our multivariate analyses of 480 Black cases, only one factor, early diagnosis age in the case, was a significant predictor of *BRCA1* and *BRCA2* mutations. Among 197 Black cases with a family history of breast cancer, first-degree family history of breast cancer, early onset in a relative, and ovarian cancer family history were all significant predictors of *BRCA1* carrier status whereas breast cancer in multiple relatives was the only significant predictor of *BRCA2* carrier status. Our findings in Black cases are somewhat comparable with those in a recent report on 43 Black families

Table 4. Multivariate model: odds of carrying a mutation in relation to demographic and familial characteristics of CARE Study participants diagnosed with breast cancer at ages 35 to 64 in five centers in the U.S.

Characteristics	All cases		White
	Univariate* OR (95% CI)	Multivariate* OR (95% CI)	Multivariate* OR (95% CI)
BRCA1			
Model I (among all cases)			
		(n = 1,623)	(n = 1,143)
Case diagnosed at age <45	9.3 (4.3-20.1)	9.5 (4.2-21.2)	8.4 (3.4-21.0)
Jewish ancestry	6.1 (2.2-16.7)	7.8 (2.6-23.8)	6.4 (2.0-20.1)
Ovarian cancer family history †	6.3 (2.8-14.2)	9.3 (3.9-22.3)	9.1 (3.4-24.4)
Breast cancer family history †,‡	2.6 (1.2-5.9)	2.4 (1.0-5.5)§	2.4 (0.9-6.3)
First-degree	4.4 (1.9-10.3)	3.8 (1.5-9.6)	3.5 (1.2-10.2)
Second-degree only	1.6 (0.6-4.3)	1.5 (0.6-4.2)	1.7 (0.6-5.2)
Model II (among cases with a family history of breast cancer)			
		(n = 858)	(n = 661)
Case diagnosed at age <45	9.7 (4.5-21.2)	8.7 (3.8-20.0)	9.0 (3.6-22.5)
Jewish ancestry	3.8 (1.4-10.8)	5.0 (1.4-17.1)	4.1 (1.3-13.4)
Ovarian cancer family history †	7.4 (2.8-19.7)	8.3 (2.5-27.9)	5.5 (1.8-17.2)
First degree relative with breast cancer	2.8 (1.3-6.2)	1.8 (0.6-5.3)	1.6 (0.5-5.3)
Breast cancer at age <45 in family †	6.1 (2.7-13.5)	4.0 (1.7-9.7)	4.5 (1.5-13.3)
Two or more relatives with breast cancer †	3.6 (1.6-7.9)	1.6 (0.6-4.3)	1.6 (0.5-5.3)
Relative with bilateral breast cancer †	2.7 (1.3-5.7)	1.4 (0.5-3.7)	1.1 (0.3-3.7)
BRCA2			
Model I (among all cases)			
		(n = 1,623)	(n = 1,143)
Case diagnosed at age <45	2.8 (1.4-5.7)	2.8 (1.3-6.0)	2.3 (0.8-6.2)
Jewish ancestry	0.6 (0.1-2.7)	0.6 (0.1-2.8)	0.4 (0.1-2.2)
Ovarian cancer family history †	2.0 (0.4-8.7)	2.3 (0.6-9.7)	3.5 (0.7-17.1)
Breast cancer family history †,‡	1.8 (0.8-4.2)	1.3 (0.5-3.2)	1.2 (0.4-3.4)
First-degree	3.0 (1.3-6.9)	2.2 (0.9-5.9)	1.8 (0.5-6.2)
Second-degree only	1.0 (0.3-3.3)	0.8 (0.2-2.4)	0.8 (0.2-2.8)
Model II (among cases with a family history of breast cancer)			
		(n = 858)	(n = 661)
Case diagnosed at age <45	2.2 (1.0-5.0)	2.5 (1.1-5.7)	2.3 (0.7-7.4)
Jewish ancestry	0.9 (0.2-5.0)	1.1 (0.2-5.6)	1.0 (0.2-5.2)
Ovarian cancer family history †	6.4 (1.4-29.8)	5.0 (0.9-28.2)	7.2 (1.1-45.8)
First degree relative with breast cancer	3.0 (1.0-9.0)	2.3 (0.8-6.9)	2.3 (0.6-8.2)
Breast cancer at age <45 in family †	3.4 (1.5-8.1)	2.3 (1.0-5.4)§	2.6 (1.0-6.7)
Two or more relatives with breast cancer †	2.6 (1.1-5.9)	1.6 (0.7-3.6)	0.9 (0.3-2.3)
Relative with bilateral breast cancer †	1.7 (0.7-4.4)	1.1 (0.5-2.7)	1.0 (0.3-3.3)

*All ORs are adjusted for sampling weights and study matching factors (age, race, and field center) with the following exceptions: models within racial/ethnic subgroups exclude race as a covariate, models within Black women and models within Jewish women exclude the variable on Jewish status, and models within age subgroups exclude the dichotomous age variable but include a continuous age variable. Univariate estimates are only adjusted for sampling weights and matching factors. Multivariate estimates are adjusted for sampling weights and matching factors plus all other family history or demographic factors listed for that model.

† Refers to either first or second degree female relatives.

‡ Two sets of models were used to derive ORs for family history of breast cancer estimated among all cases. The first model estimated ORs for the odds of carrying a mutation in relation to having any first or second degree female relative with breast cancer. A separate but otherwise similar model was used to estimate the separate ORs for first degree and second degree only family history of breast cancer.

§ CI excludes 1.0.

at high risk (31), in that both studies found early onset age and larger number of affected relatives to be predictive of carrying a mutation in one of the two genes. Both studies found ovarian cancer to be less common in Black versus White families; nonetheless, our data suggested that ovarian cancer family history might be predictive of *BRCA1* carrier status in Black women, although this was based on only one carrier. Among White cases with a family history, early diagnosis in a case, and/or in a relative, Jewish ancestry, and family history of ovarian cancer were predictive of being a *BRCA1* carrier; there were two predictors of *BRCA2*, ovarian cancer family history (a strong predictor), and multiple relatives with breast cancer (a modest predictor). To our

Table 4. Multivariate model: odds of carrying a mutation in relation to demographic and familial characteristics of CARE Study participants diagnosed with breast cancer at ages 35 to 64 in five centers in the U.S. (Cont'd)

Black	Jewish	Age <45 at diagnosis	Age 45+ at diagnosis
Multivariate* OR (95% CI)	Multivariate* OR (95% CI)	Multivariate* OR (95% CI)	Multivariate* OR (95% CI)
(n = 480)	(n = 86)	(n = 546)	(n = 1,077)
12.3 (2.5-61.1)	23.6 (2.3-246.0)	—	—
—	—	7.9 (2.2-27.9)	11.3 (2.0-62.8)
3.4 (0.7-17.8)	6.1 (0.3-113.8)	8.0 (3.0-21.1)	13.6 (2.4-77.9)
1.9 (0.4-8.5)	1.1 (0.1-9.6)	2.7 (1.1-6.7)	1.8 (0.5-7.2)
4.4 (0.8-23.0)	1.5 (0.1-15.5)	4.0 (1.5-10.5)	4.0 (1.1-14.8)
0.6 (0.1-3.5)	0.8 (0.0-14.5)	2.1 (0.7-6.0)	—
(n = 197)	(n = 51)	(n = 271)	(n = 587)
3.5 (0.6-19.6)	42.0 (2.1-823.6)	—	—
—	—	9.7 (1.8-52.7)	1.5 (0.2-12.0)
257.6 (11.7-5682.9)	25.0 (1.3-496.0)	10.4 (2.3-45.7)	1.3 (0.2-7.8)
7.9 (1.4-44.5)	0.2 (0.0-3.0)	1.2 (0.3-4.6)	—
15.2 (1.3-172.4)	14.1 (2.0-100.3)	3.7 (1.2-11.9)	5.5 (1.1-28.9)
4.9 (0.4-65.7)	1.4 (0.1-17.2)	2.4 (0.6-8.7)	1.1 (0.2-5.4)
2.6 (0.5-12.9)	5.5 (0.2-172.7)	1.6 (0.4-5.6)	0.9 (0.2-4.3)
(n = 480)	(n = 86)	(n = 546)	(n = 1,077)
3.7 (1.1-12.2)	3.1 (0.2-54.0)	—	—
—	—	0.7 (0.1-6.7)	0.4 (0.0-3.9)
—	—	1.4 (0.3-7.0)	4.0 (0.6-28.4)
2.0 (0.4-9.3)	—	1.6 (0.5-5.4)	1.0 (0.3-3.9)
3.1 (0.7-14.0)	—	3.3 (0.8-12.8)	1.4 (0.3-5.6)
0.9 (0.1-10.2)	—	0.8 (0.2-3.8)	0.7 (0.1-3.9)
(n = 197)	(n = 51)	(n = 271)	(n = 587)
2.0 (0.6-7.0)	3.5 (0.3-42.2)	—	—
—	—	1.1 (0.1-19.9)	0.6 (0.1-6.9)
—	—	3.3 (0.5-23.6)	11.9 (1.3-104.7)
2.7 (0.4-17.2)	—	2.3 (0.6-9.5)	1.9 (0.5-7.9)
2.1 (0.5-8.2)	—	4.7 (1.3-16.4)	1.1 (0.3-3.9)
5.0 (1.2-20.8)	—	3.9 (1.0-16.0)	1.0 (0.3-3.5)
1.4 (0.3-5.8)	—	1.3 (0.4-4.7)	0.5 (0.1-2.1)

knowledge, this is the largest study to date of *BRCA1/BRCA2* in Black women with breast cancer, and is the first to present multivariate analyses of predictors of mutation status in a population-based setting.

Among the Jewish women with breast cancer in this study (n = 86), 10.2% carried a *BRCA1* mutation and 1.1% carried a *BRCA2* mutation, in general agreement with earlier reports (2, 4, 33). All mutations observed in Jewish cases were confined to the three previously reported founder mutations (*185delAG, 5382insC,* and *6174delT*). Multivariate analyses identified three strong, significant predictors of *BRCA1* mutation status in Jewish cases, diagnosis at ages 35 to 44 in the cases, early diagnosis age in a relative, and family history of ovarian cancer. Because the CARE Study questionnaire did not assess ethnicity, the religion in which women were raised served as a surrogate for Jewish ancestry, likely misclassifying a small proportion of women.

Strengths and limitations. This is the largest population-based study of *BRCA1/BRCA2* to date. The population-based design, wider age range, and inclusion of both Black and White women allow a more comprehensive portrayal of the frequency of mutations in the general population than has been available. Despite the generous sample size, the number of mutations detected was fairly small, resulting in some uncertainty around estimates. The enhanced generalizability of our results could be offset to the extent that those who participated differ from those who did not. Fortunately, study response proportions were high and met or exceeded those in similar studies. In addition, the genotyping methodology, DHPLC, was state of the art when the study began (44, 45), and remains, short of complete sequencing, the most comprehensive high-throughput mutation detection method (16). DHPLC is not suitable for the detection of large genomic deletions (46), and although their prevalence remains unclear and may vary across populations

Table 5. Multivariate model: odds of carrying a mutation in either *BRCA1* or *BRCA2* in relation to demographic and familial characteristics of CARE Study participants diagnosed with breast cancer at ages 35 to 64 in five centers in the U.S.

Characteristics	*BRCA1* or *BRCA2*						
	All cases		White	Black	Jewish	Age <45 at diagnosis	Age 45+ at diagnosis
	Univariate*	Multivariate*	Multivariate*	Multivariate*	Multivariate*	Multivariate*	Multivariate*
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Model I (among all cases)							
	(n = 1,623)		(n = 1,143)	(n = 480)	(n = 86)	(n = 546)	(n = 1,077)
Case diagnosed at age <45	4.9 (2.9-8.1)	4.8 (4.2-21.2)	4.4 (2.2-8.6)	5.3 (2.0-13.8)	16.3 (2.6-1,001.6)	—	—
Jewish ancestry	3.1 (1.3-7.2)	3.5 (1.4-8.6)	2.8 (1.1-7.4)	—	—	4.5 (1.5-13.1)	2.3 (0.5-12.0)
Ovarian cancer family history †	4.3 (2.1-9.0)	5.4 (2.6-11.5)	6.4 (2.7-15.3)	1.5 (0.3-8.0)	4.9 (0.4-63.2)	5.1 (2.2-11.8)	6.0 (1.5-23.3)
Breast cancer family history †,‡	2.2 (1.2-4.0)	1.8 (1.0-3.4)	1.8 (0.8-3.8)	1.9 (0.6-6.0)	1.4 (0.2-10.3)	2.3 (1.1-4.9)	1.3 (0.4-3.5)
First-degree	3.6 (1.9-6.7)	3.0 (1.5-5.9)	2.8 (1.2-6.4)	3.3 (1.1-10.5)	2.1 (0.3-16.8)	3.7 (1.6-8.4)	2.1 (0.7-6.0)
Second-degree only	1.3 (0.6-2.8)	1.1 (0.5-2.5)	1.3 (0.5-3.0)	0.8 (0.1-4.2)	0.8 (0.0-13.7)	1.6 (0.7-3.9)	0.6 (0.1-2.7)
Model II (among cases with a family history of breast cancer)							
	(n = 858)		(n = 661)	(n = 197)	(n = 51)	(n = 271)	(n = 587)
Case diagnosed at age <45	4.7 (2.6-8.3)	4.5 (2.4-8.4)	4.7 (2.1-10.2)	2.6 (0.9-7.4)	14.8 (2.4-91.0)	—	—
Jewish ancestry	2.4 (1.0-6.0)	2.9 (1.1-7.9)	2.6 (0.9-6.9)	—	—	6.3 (1.4-29.0)	1.0 (0.2-5.9)
Ovarian cancer family history †	7.4 (3.0-18.4)	7.0 (2.5-19.9)	5.9 (1.9-18.1)	21.5 (2.2-214.9)	5.9 (0.4-79.0)	8.3 (2.1-33.1)	5.8 (0.8-43.5)
First degree relative with breast cancer	2.9 (1.5-5.6)	2.0 (0.9-4.3)	1.9 (0.7-4.7)	3.3 (0.9-11.8)	1.3 (0.1-15.1)	1.4 (0.5-4.3)	3.2 (0.8-13.3)
Breast cancer at age <45 in family †	4.6 (2.6-8.3)	3.1 (1.7-5.7)	3.5 (1.6-7.4)	3.7 (1.1-11.9)	3.1 (0.5-18.6)	3.9 (1.6-9.6)	2.0 (0.8-5.1)
Two or more relatives with breast cancer †	3.1 (1.7-5.5)	1.6 (0.8-3.0)	1.2 (0.5-2.9)	4.9 (1.3-18.1)	1.0 (0.2-5.8)	2.7 (1.0-7.7)	1.0 (0.4-2.6)
Relative with bilateral breast cancer †	2.2 (1.2-4.0)	1.3 (0.7-2.5)	1.1 (0.5-2.6)	1.7 (0.6-5.2)	3.0 (0.4-21.1)	1.5 (0.6-4.1)	0.6 (0.2-1.9)

*All ORs are adjusted for sampling weights and study matching factors (age, race, and field center) with the following exceptions: models within racial/ethnic subgroups exclude race as a covariate, models within Black women and models within Jewish women exclude the variable on Jewish status, and models within age subgroups exclude the dichotomous age variable but include a continuous age variable. Univariate estimates are only adjusted for sampling weights and matching factors. Multivariate estimates are adjusted for sampling weights and matching factors plus all other family history or demographic factors listed for that model.

† Refers to either first or second degree female relatives.

‡ Two sets of models were used to derive ORs for family history of breast cancer estimated among all cases. The first model estimated ORs for the odds of carrying a mutation in relation to having any first or second degree female relative with breast cancer. A separate but otherwise similar model was used to estimate the separate ORs for first degree and second degree only family history of breast cancer.

(47, 48), it is likely that we underestimated mutation frequency. Prediction of mutation status may be improved by a Bayesian-Mendelian approach (49), in which carrier probabilities are calculated using the full pedigree structure instead of selected family history features. This approach requires knowledge of the penetrance function for these genes, an obstacle that can be overcome in this study because of its population-based sampling scheme (50). Such analyses are under way.[14]

Conclusion. Through the inclusion of women up to 64 years of age, and a large number of White and Black women in a population-based setting, this study provides new information on the prevalence and predictors of *BRCA1* and *BRCA2* mutation carrier status. *BRCA1* mutation frequency was slightly higher in White versus African-American cases, and was substantially higher in Jewish cases; *BRCA2* mutation frequency was slightly but nonsignificantly greater in Black versus White cases. Mutation frequency for both genes decreased with age. A large number of factors were individually associated with the odds of carrying a *BRCA1* mutation; multivariate analyses distinguished the very strong effect of early diagnosis age, Jewish ancestry, ovarian cancer family history, and early onset in a relative from the more modest or absent effects of other factors. Although a number of factors were individually associated with *BRCA2* mutation status, few remained significant in multivariate analyses and the magnitudes of effects were lower overall than for *BRCA1*. Age at onset was the single most important predictor for *BRCA2* status among all cases with and without family history, and early onset age in a relative was additionally predictive among cases with a family history. Some variation in associations was observed across subgroups.

[14] L. Chen, Semiparametric analysis of failure time data from case-control family studies on candidate genes [dissertation], University of Washington, Department of Biostatistics, 2005.

These findings show the relative importance of specific family history and other characteristics in predicting mutation carriership, and may serve to alert women and their clinicians of indicators of a potentially heightened likelihood of carrying a mutation. Of note, the results presented here summarize aggregate population results for individual risk factors and do not consider the integrated context of each woman's complete family history structure. Thus, it should not be assumed that the presence (or absence) of any one factor in a woman's profile necessarily equates to a high (or low) likelihood of carrying a mutation. Lastly, whereas the emphasis in this report is on gaining insights regarding the predictors of being a mutation carrier, these results also serve as a continued reminder that the majority of women with breast cancer, even those with a first-degree family history, do not carry mutations in these genes.

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