Prevalence of *BRCA1* Mutation Carriers among U.S. Non-Hispanic Whites

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Abstract

Data from several countries indicate that 1% to 2% of Ashkenazi Jews carry a pathogenic ancestral mutation of the tumor suppressor gene *BRCA1*. However, the prevalence of *BRCA1* mutations among non-Ashkenazi Whites is uncertain. We estimated mutation carrier prevalence in U.S. non-Hispanic Whites, specific for Ashkenazi status, using data from two population-based series of San Francisco Bay Area patients with invasive cancers of the breast or ovary, and data on breast and ovarian cancer risks in Ashkenazi and non-Ashkenazi carriers. Assuming that 90% of the *BRCA1* mutations were detected, we estimate a carrier preva-lence of 0.24% (95% confidence interval, 0.15-0.39%) in non-Ashkenazi Whites, and 1.2% (95% confidence interval, 0.5-2.6%) in Ashkenazim. When combined with U.S. White census counts, these prevalence estimates suggest that approximately 550,513 U.S. Whites (506,206 non-Ashkenazim and 44,307 Ashke-nazim) carry germ line *BRCA1* mutations. These estimates may be useful in guiding resource allocation for genetic testing and genetic counseling and in planning preventive interventions. (Cancer Epidemiol Biomarkers Prev 2004;13(12):2078−83)

Introduction

Studies of Ashkenazi Jews in the United States, Australia, and Israel indicate that approximately 1% to 2% of these populations carry an ancestral mutation (185delAG or 5382insC) of the tumor suppressor gene *BRCA1* (1-3). These prevalence estimates were obtained by testing DNA samples from individuals unselected for personal or family history of cancer. Carrier prevalence among U.S. non-Ashkenazi Whites is thought to be substantially lower, but precise estimates are not available. Indeed, because prevalence is so low, the number of unselected individuals needed for such estimates would be prohib-itively large. However, precise prevalence estimates are needed to guide resource allocation for genetic testing and genetic counseling (4) and to plan screening studies and preventive interventions.

Here we present estimates of mutation carrier preva-lence among U.S. non-Hispanic Whites, specific for Ashkenazi heritage. We obtained these estimates by com-bining carrier prevalences among two population-based series of patients with breast and ovarian cancer with published estimates of cumulative risks for breast and ovarian cancer in mutation carriers and noncarriers (5, 6).

Materials and Methods

Patient Populations. Women diagnosed with breast or ovarian cancer were identified through the population-based cancer registry covering nine counties of the Greater San Francisco Bay area and operated by the Northern California Cancer Center as part of the Surveillance, Epidemiology and End Results Program of the National Cancer Institute and the California Cancer Registry. Patients with breast cancer were enrolled in the Northern California component of the Breast Cancer Family Regis-try, a consortium funded by the U.S. National Cancer Institute. Eligible patients were women diagnosed with invasive or *in situ* breast cancer at ages 20 to 64 years during the period January 1, 1995, to September 30, 1998. Participants were recruited using a two-stage sampling design that oversamples patients whose characteristics suggest an inherited basis for their cancers (7, 8). This sampling design provides unbiased estimates of carrier prevalence in the San Francisco Bay Area population of breast cancer cases that have greater precision than those obtained from a simple random sample of the same size. In stage 1, we screened patients by telephone to classify them into one of two categories: category A (patients whose cancers are likely to be hereditary) and category B (all other patients), hereafter called "hereditary" and "nonheredi-tary" categories. In stage 2, we invited all patients in cat-egory A and a random sample of 2.5% of those in category B to enroll in the Breast Cancer Family Registry. Category A patients were those who met at least one of the following criteria: (*a*) breast cancer diagnosis before age 35 years; (*b*) bilateral breast cancer with first diagnosis before age 50 years; (*c*) prior ovarian or childhood cancer; (*d*) at least one first-degree relative with breast or ovarian cancer.

Patients with ovarian cancer were enrolled in the Familial Registry of Ovarian Cancer, a research project funded by the National Cancer Institute. Eligible patients were women diagnosed with invasive epithelial ovarian cancer or epithelial tumors of low malignant potential at ages 20 to 64 years during the period March 1, 1997, through July 31, 2001. Patients were identified by the cancer registry within 1 month of diagnosis using rapid case ascertainment and were invited to participate in the study regardless of their personal or family cancer histories.

Participants from both studies provided information on family history and demographic and life-style characteristics, as well as blood or mouthwash samples for DNA analysis. The present analysis is restricted to non-Hispanic White patients with invasive breast or ovarian cancer who were tested for *BRCA1* mutations. Prevalence estimates based on the breast cancer data were obtained by weighting the counts of patients in each of the two categories A and B, with the weight for a category inversely proportional to the fraction of all screened patients in that category who were tested. In the ovarian cancer study, patients whose cancers are likely to be hereditary (i.e., ovarian cancer diagnosis before age 40 years, prior breast cancer, and at least one first-degree relative with ovarian cancer or with breast cancer diagnosed before age 50 years) were tested for mutations at a slightly higher frequency (79%) than were other patients (69%). To reduce potential selection bias in mutation prevalence estimates that might arise from this differential testing rate, we also classified patients with ovarian cancer as either hereditary (category A) or nonhereditary (category B), and weighted patient counts in each category in proportion to the inverse of the testing rate for the category.

Further details concerning study protocol can be found in John et al. (9) for the breast cancer study and McGuire et al. (10) for the ovarian cancer study. Both study protocols were approved by all the institutions involved with the research. These included the Northern California Cancer Center, Stanford University, and the Dana-Farber Cancer Institute (for the breast cancer study) and Stanford University, the Northern California Cancer Center, and the Roswell Park Cancer Institute (for the ovarian cancer study).

Laboratory Analysis. Samples of heparinized, peripheral blood or buccal cells from mouthwash rinse were obtained in study participants' homes or at other locations of their convenience. Specimens were shipped overnight via Federal Express courier to the Coriell Institute for Medical Research (breast cancer study) or the Roswell Park Cancer Institute (ovarian cancer study). Genomic DNA was isolated from blood leukocytes using the Puregene kit (Gentra Systems, Minneapolis, MN). For the patients with ovarian cancer, genomic DNA was also isolated from exfoliated cells in mouthwash samples according to Lum and Marchand (11). For patients with breast cancer, DNA from blood leukocytes was tested for BRCA1 variants using two-dimensional gene scanning (12, 13). The entire *BRCA1* coding region and parts of the introns were amplified in a two-step PCR process involving six individual multiplex reactions. For patients with ovarian cancer, DNA from blood leukocytes or mouthwash samples was tested for BRCA1 variants using single-strand conformation polymorphism (SSCP; refs. 14, 15). For SSCP, the entire coding region of

BRCA1 (exons 2, 3, and 5-24) and splice junctions were amplified using 41 primer pairs. DNA variants in exon 11 of *BRCA1* were also assessed by the protein truncation test (16). Primer structures and conditions for DNA amplification, SSCP, and protein truncation test are available on request by e-mail (richard.dicioccio@roswellpark.org). Amplification products with DNA variants detected by SSCP or protein truncation test were purified for direct DNA sequencing to identify mutations (16).

The methods of both groups permit detection of mutations and polymorphisms in BRCA1 coding regions as well as splice-site mutations. Patients were considered mutation carriers if testing indicated a pathogenic variant according to guidelines described by Couch et al. (17). Such mutations include small deletions or insertions causing a frameshift and generation of a premature stop codon, nonsense mutations, splice-site mutations predicted to cause aberrant splicing and generation of a premature stop codon, and missense mutations in the ring-finger domain of the gene. Among the 18 carriers with breast cancer, there were 10 frameshift, 4 nonsense, 2 missense, and 2 splice-site mutations. Among the 29 carriers with ovarian cancer, there were 20 frameshift, 4 nonsense, 4 missense, and 1 splice-site mutation. Regulatory mutations outside of the coding region and splice junctions and large genomic rearrangements are not detected by the methods used here. Publications screening for these mutations are limited to members of families with a high prior probability of carrying a *BRCA1* mutation, and the prevalence of these mutations in unselected populations is unknown (18-21).

Statistical Analysis. We estimated the prevalence of BRCA1 mutation carriers among subgroups of patients with breast and ovarian cancer defined by age at diagnosis, Ashkenazi ancestry and family history (presence of breast or ovarian cancer in a first-degree relative). To account for differential *BRCA1* testing frequencies of patients in hereditary and nonhereditary categories A and B, we estimated prevalences using Horvitz-Thompson estimating equations (7, 8). The Horvitz-Thompson prevalence estimate for a given subgroup of cancer patients is

$$\hat{\theta} = \frac{p_A^{-1} n_A + p_B^{-1} n_B}{p_A^{-1} \bar{N}_A + p_B^{-1} \bar{N}_B} \qquad (A)$$

Here p_A and p_B are the testing rates in categories A and B, respectively. In addition, $\bar{N}_A$ and n_A are the numbers of tested patients and identified carriers, respectively, in the subgroup that lies in category A, with $\bar{N}_B$ and n_B defined similarly. $\hat{\theta}$ is an unbiased estimate of the carrier detection rate in all patients in the subgroup (tested or not) provided the carrier statuses of tested patients in categories A and B represent those of all patients in these categories. We estimated the variance of $\hat{\theta}$ as $\sigma^2 = X_2 / X_1^2$, where

$$X_r = \frac{p_A^{-r} n_A + p_B^{-r} n_B}{\hat{\theta}^2} + $$
$$\frac{p_A^{-r} (\bar{N}_A - n_A) + p_B^{-r} (\bar{N}_B - n_B)}{(1 - \hat{\theta})^2}, \; r = 1,2 \qquad (B)$$

Had all patients in both categories been tested, that is, $p_A = p_B = 1$, these formulae for $\hat{\theta}$ and $\hat{\sigma}^2$ would reduce to the usual ones for a simple binomial proportion.
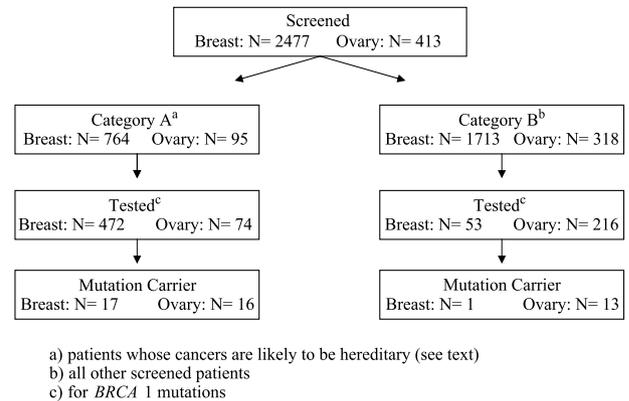
We also estimated mutation prevalence in the general U.S. White population specific for Ashkenazi Jewish status. The Horvitz-Thompson estimating equations for these estimates are described in Appendix 1. We obtained these prevalence estimates using (*a*) only the patients with breast cancer, (*b*) only the patients with ovarian cancer, and (*c*) the combined data from both patient groups. We calculated the estimate based on the combined group as weighted average of the two site-specific estimates, with weights inversely proportional to their variances. To account for imperfect test sensitivity, we multiplied the estimates $\hat{\theta}$ by various prespecified values γ^{-1}, where $0 < \gamma \leq 1$ represents test sensitivity.

We computed confidence limits for all prevalence estimates using the logistic transform, which increases coverage accuracy by decreasing skewness in the distribution of estimates.

Results

We were able to screen 2,477 (88%) of 2,811 potentially eligible White patients with breast cancer and 413 (89%) of 465 potentially eligible White patients with ovarian cancer. Figure 1 shows the numbers of screened and tested patients in categories A and B for each of the two cancer sites. Of the 2,477 White patients with breast cancer screened, 764 were classified into category A and the remaining 1,713 were classified into category B. All 764 category A patients were invited to provide blood samples; of these, 472 ($p_A = 62\%$) provided DNA and were tested for *BRCA1* mutations. Of these 472 patients, 17 were identified as carriers. Of the 1,713 category B patients, 83 (5%) were invited to participate, and 53 [$p_B = 100 \times (53/1,713) = 3\%$] provided DNA and were tested. Among these 53 patients, one was identified as a carrier. Of the 413 White patients with ovarian cancer screened, 95 were classified into category A and the remaining 318 were classified into category B. Of the 95 category A patients, 77 were invited to give blood and of these, 74 provided DNA and were tested for BRCA1 mutations, yielding a sampling fraction of $p_A = 100 \times (74/95) = 78\%$. Among these 74 patients, 16 were identified as carriers. Blood samples were requested from 228 of the 318 category B patients and of these, 218 provided DNA and were tested, yielding a sampling fraction of $p_B = 100 \times (218/318) = 69\%$. Among these 218 patients, 13 were identified as carriers.

Table 1 shows weighted estimates of *BRCA1* mutation prevalence among patients with breast and ovarian cancer according to age at diagnosis, Ashkenazi ancestry, and family history. Overall, patients with ovarian cancer are more than thrice more likely to carry a *BRCA1* mutation than are patients with breast cancer (9.6% versus 2.4%, respectively). Prevalence is higher among Ashkenazim than non-Ashkenazim and decreases with age at diagnosis. Although family history–negative patients are less likely than family history–positive patients to carry a mutation, carrier prevalences still are high among them, particularly those with ovarian cancer (7%). Indeed, more than half of carriers with either

a) patients whose cancers are likely to be hereditary (see text)
b) all other screened patients
c) for *BRCA 1* mutations

Figure 1. White Non-Hispanic patients with invasive cancer of the breast or ovary.

cancer are estimated to have no first-degree relative with breast or ovarian cancer (data not shown).

Table 2 shows estimates of carrier prevalence in the general U.S. non-Hispanic White population, specific for Ashkenazi heritage. Estimates are shown corresponding to test sensitivities of 90% and 65%. For each test sensitivity and each Ashkenazi subgroup, the table shows an estimate based only on the breast cancer data, one based only on the ovarian cancer data, and a combined estimate obtained as a weighted average of the two site-specific estimates. Among the Ashkenazim, carrier prevalence estimated from the ovarian cancer data is higher than that estimated from the breast cancer data, although the 95% confidence intervals (95% CI) for the two estimates overlap. Assuming a test sensitivity of 90%, we obtained a combined estimate of 1.2% prevalence (95% CI, 0.5-2.6%).

For U.S. non-Ashkenazim, the combined prevalence estimate is 0.26% (95% CI, 0.15-0.39%) when 90% test sensitivity is assumed. Thus, 1 in 400 U.S. non-Hispanic Whites without Ashkenazi heritage is estimated to carry a mutation. If test sensitivity is 65%, the combined estimate is 0.34% (95% CI, 0.21-0.55%), or 1 carrier per 300 individuals.

According to the 2000 U.S. census, the U.S. population includes 211,460,626 non-Hispanic Whites, of whom 3,702,400 are Jewish. We combined these population counts with the prevalence estimates in Table 2 to estimate the numbers of U.S. non-Hispanic White carriers, specific for Ashkenazi ancestry. When test sensitivity is specified as 90%, we estimate a total of $3,702,400 \times 0.012 = 44,307$ Ashkenazi carriers, assuming that the U.S. Jewish population consists entirely of Ashkenazim. The number of non-Ashkenazi carriers is approximately $(211,460,626 - 3,702,400) \times 0.0024 = 506,206$, giving an estimated total of 550,513 non-Hispanic White carriers. The corresponding estimates for 65% test sensitivity are 61,737 Ashkenazi and 700,901 non-Ashkenazi carriers, for a total of 762,638 non-Hispanic White carriers.

Discussion

We have presented estimates of *BRCA1* mutation carrier prevalence among U.S. non-Hispanic Whites, specific

Table 1. Numbers of BRCA1 mutation carriers detected among non-Hispanic White San Francisco Bay Area patients with invasive cancers of the breast or ovary, by Ashkenazi heritage, age, and family history

	Breast cancer patients							Ovarian cancer patients						
	No. tested			No. positive			Prevalence,* % (95% CI)	No. tested			No. positive			Prevalence, % (95% CI)
	A[†]	B	Total	A	B	Total		A	B	Total	A	B	Total	
All patients	472	53	525	17	1	18	2.4 (.8-6.9)	74	216	290	16	13	29	9.6 (6.7-13.5)
Ashkenazi	33	3	36	5	0	5	5.4 (1.7-15.5)	6	22	28	3	3	6	20.6 (9.5-39.1)
Non-Ashkenazi	439	50	489	12	1	13	2.2 (0.6-7.4)	68	194	262	13	10	23	8.4 (5.7-12.4)
Age (y)														
<35	79	0	79	6	0	6	7.6 (3.5-15.9)	12	0	12	1	0	1	8.3 (1.2-41.3)
35-59	147	13	160	7	1	8	6.6 (1.5-24.3)	33	69	102	12	8	20	18.9 (12.5-27.5)
50+	246	40	286	4	0	4	0.4 (0.1-1.0)	29	147	176	3	5	8	4.4 (2.2-8.6)
Family history[‡]														
Positive	330	4	334	13	0	13	3.2 (1.8-5.6)	37	28	65	11	2	13	19.2 (11.5-30.4)
Negative	142	49	191	4	1	5	2.1 (0.4-10.3)	37	188	225	5	11	16	7.0 (4.3-11.1)

*Weighted estimate, described in text.
[†] See text for definitions of category A and category B patients.
[‡] First-degree relative with breast cancer or ovarian cancer.

for Ashkenazi heritage. We obtained these estimates by combining data from two population-based series of patients with breast and ovarian cancer with published estimates of cumulative risks for breast and ovarian cancer in mutation carriers and noncarriers (5, 6). The 95% CIs for our prevalence estimates reflect the uncertainty in these cumulative risk estimates.

We found a prevalence estimate of 1.2% among Ashkenazim, which agrees well with those obtained in other Ashkenazi populations in the United States (1), Australia (2), and Israel (3). We also found that approximately 0.24% of U.S. non-Hispanic Whites without Ashkenazi heritage carry a mutation, with 95% confidence limits of 0.15% to 0.39%. This finding represents the first precise estimate for this population. The estimate assumes 90% test sensitivity, which probably is too high; indeed, we know little about the prevalence of mutations that cannot be detected by PCR amplification. Thus, actual carrier prevalence may be somewhat higher. Nevertheless, the non-Ashkenazi prevalence estimate of 0.24% is more than double the 0.07% to 0.09% prevalence in the United Kingdom population estimated by the Anglican Breast Cancer Group (22), which was based on eight BRCA1 mutation carriers in 1,220 patients with breast cancer. This difference, if not due to chance or bias, could reflect differences in the ethnic backgrounds of the U.S. and UK populations.

We have also presented estimates of *BRCA1* mutation carrier prevalence in various subgroups of patients diagnosed with breast or ovarian cancer. These estimates agree well with those obtained in other population-based series of cancer cases in the United States and Canada. The prevalence estimate of 2.4% (95% CI, 0.8-6.9%) among patients with breast cancer is similar to that of 3.3% (95% CI, 0-72%) found among White patients with breast cancer in a population based series from North Carolina (23). The tighter CI for the present estimate is due to the larger sample sizes (18 carriers among 525 patients with breast cancer in the present study compared to 3 carriers among 211 patients in the previous study) and to some increases in statistical efficiency gained from the two-stage sampling design (24). The prevalence estimate of 7.6% (95% CI, 3.5-15.9) for cases diagnosed under age 35 years is similar to the estimate of 6.2% (95% CI, 3.2-10.6%) found for a similar group of patients with breast cancer from the Seattle, Washington area (25).

The estimated carrier prevalence of 9.6% (95% CI, 6.7-13.5%) among patients with ovarian cancer is also consistent with other patient series. In a population-based case-control study of ovarian cancer conducted in Canada, Risch et al. (26) found that 10.3% of patients diagnosed before age 50 years and 5.5% of those diagnosed between ages 50 and 60 years carried such a mutation. The high prevalence of mutation carriers among patients with ovarian cancer, even those without

Table 2. Estimated BRCA1 mutation carrier prevalence (%) in U.S. non-Hispanic Whites, by Ashkenazi heritage

Test sensitivity (%)	Study	Prevalence,* % (95% CI)	
		Ashkenazi Jewish	Non-Ashkenazi Jewish
90	Breast cancer	1.0 (0.4-2.6)	0.22 (0.06-0.76)
	Ovarian cancer	3.2 (1.0-9.5)	0.25 (0.15-0.42)
	Both studies	1.2 (0.5-2.6)	0.24 (0.15-0.39)
65	Breast cancer	1.5 (0.6-3.8)	0.31 (0.09-1.05)
	Ovarian cancer	4.9 (1.5-15.4)	0.34 (0.20-0.58)
	Both studies	1.7 (0.7-3.8)	0.34 (0.21-0.55)

*Weighted estimate, described in text.

a family history of breast or ovarian cancer, has particular relevance to patients and their clinicians. In particular, patients with ovarian cancer were more than thrice more likely than patients with breast cancer to carry a *BRCA1* mutation (9.6% versus 2.4%). Moreover, carrier prevalence was 7% among patients with ovarian cancer having no first-degree relative with either breast or ovarian cancer.

Some limitations of the present study must be considered in interpreting its findings. It is infeasible to evaluate BRCA1 mutation carrier prevalence in a population-based sample of unselected, non-Ashkenazi individuals because mutations are so rare in this population. Instead, we obtained our estimates by combining prevalences observed in population-based samples of breast and ovarian cancer cases with published penetrance estimates. Consequently our estimates are sensitive to misspecification of penetrance in the Ashkenazi and non-Ashkenazi populations. The good agreement between the present and previous prevalence estimates among Ashkenazim provide some reassurance that the penetrance estimates of Struewing et al. (5) are accurate. In addition, because risk estimates tend to be less sensitive to parameter misspecification than are estimates of absolute risk, we estimated carrier penetrances for non-Ashkenazim as the product of population incidence rates times the relative risk estimates obtained from a large meta-analysis of cancer risk in first-degree relatives of unselected patients with breast and ovarian cancer (6). Our CIs for prevalence also include uncertainty in these relative risk estimates.

A second limitation pertinent to all estimates of mutation carrier prevalence is insensitivity of the laboratory tests used to detect mutations. The two-dimensional gel test we used for the patients with breast cancer has done well in a validation study in which direct DNA sequencing was used as the standard (27). The SSCP test we used for the patients with ovarian cancer has been found to miss certain mutations (27). To address this issue we augmented the test with the protein truncation test for exon 11 of the gene. Nevertheless, both tests are likely to miss large deletions and certain other types of gene inactivation. To account for this insensitivity, we computed prevalence estimates corresponding to a range of test sensitivities.

Counterbalancing these limitations are several strengths of the study. These include the population-based assessment of carrier prevalence in an ethnically homogeneous group of patients with breast and ovarian cancer, and the large numbers of carriers identified compared to previous studies, allowing more precise estimates. The assessment of carrier prevalence in non-White populations is part of future planned work.

In conclusion, the prevalence estimates presented here for non-Hispanic Whites with and without Ashkenazi ancestry should be useful in guiding resource allocation for counseling, disease prevention, and disease detection in these populations.

Appendix A

Here we describe estimates of *BRCA1* mutation carrier prevalence in U.S. non-Hispanic Whites, specific for Ashkenazi heritage, using (*a*) the breast cancer data and (*b*) the ovarian cancer data (a total of four prevalence estimates). We illustrate the calculations by considering prevalence among non-Ashkenazim based on the breast cancer data.

Among the N_A screened patients with breast cancer in the hereditary category A, let $\bar{N}_A$ denote the number tested, and let n_A denote the number identified as mutation carriers. Define N_B, $\bar{N}_B$, and n_B similarly for the nonhereditary patients. Let $p_A = \bar{N}_A/N_A$ and $p_B = \bar{N}_B/N_B$ denote the testing frequencies in the two categories. We let $n = p_A^{-1} n_A + p_B^{-1} n_B$ and $N = p_A^{-1} \bar{N}_A + p_B^{-1} \bar{N}_B$ represent the expected numbers of carriers and patients, respectively, who might have been accrued had we tested all screened patients. We estimate the carrier prevalence θ among U.S. White non-Ashkenazim by maximizing the Horvitz-Thompson pseudo-likelihood function

$$L(\theta) = q(\theta)^n [1 - q(\theta)]^{N-n} \tag{C}$$

Here $q(\theta)$ denotes the probability that a non-Ashkenazi White woman carries a mutation, given that she has been diagnosed with breast cancer before age 65 years. We used Bayes rule to write $q(\theta) = \theta \Pr(D|\text{carrier})/\Pr(D)$, where D is the event of developing breast cancer before age 65 years. We used age-specific incidence rates for non-Hispanic White women in California in the period 1995-1999 (28) to calculate the cumulative probability $\Pr(D)$ of developing breast cancer by age 65 years. We estimated the corresponding cumulative risk $\Pr(D|\text{carrier})$ in carriers by multiplying the California incidence rates by the age-specific relative risks of Antoniou et al. (6).

We did similar calculations to estimate prevalence θ among U.S. White Ashkenazim. Here, however, we used the data of Struewing et al. (5) to estimate cumulative breast cancer risks $\Pr(D|\text{carrier})$ in carriers and $\Pr(D|\text{noncarrier})$ in noncarriers, and used these values in the formula

$$q(\theta) = \frac{\theta \Pr(D|\text{carrier})}{\theta \Pr(D|\text{carrier}) + (1 - \theta) \Pr(D|\text{noncarrier})} \tag{D}$$

We estimated the variance of each pseudo-likelihood estimate $\hat{\theta}$ using the formulae given in Whittemore and Halpern (8). For these variance estimates, we used the delta method to allow for uncertainty in the penetrance estimates of Antoniou et al. (6) and Struewing et al. (5). For the non-AJ estimates, we combined incidence rates with age-specific estimates of log relative risk and their estimated covariance matrix obtained from Antoniou.[5] For the AJ estimates, we inferred variance estimates for age-specific risks from the bootstrapped 95% CIs used by Struewing et al. (5), which we obtained from the authors.[6]

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[5] A. Antoniou, personal communication.
[6] J.P. Struewing et al., personal communication.

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