

The Lifetime Risks of Breast Cancer in Ashkenazi Jewish Carriers of *BRCA1* and *BRCA2* Mutations

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Abstract

Several studies using families with multiple occurrences of breast cancer have provided evidence for a very high lifetime penetrance in carriers of *BRCA1* or *BRCA2* mutations. However, there are reasons to suspect that the estimates of penetrance from studies of cancer families may be inflated. Access to the genotypes of incident cases of breast cancer in three hospitals and from a large series of unaffected survey participants provided the basis for direct estimation of the age-specific relative risks attributable to these mutations, and the resulting lifetime penetrance, without any reference to familial aggregation of cancer. Cases were identified from incident series of Jewish patients treated for primary breast cancer at the three hospitals. Control data were obtained from the large series of Jewish women recruited in the Washington, D.C., area by investigators at the National Cancer Institute and limited to 3434 women with no previous history of breast or ovarian cancer. All subjects were genotyped for the three mutations that are relatively common in Ashkenazi Jews, namely 185delAG and 5382 insC in *BRCA1* and 6174delT in *BRCA2*. For *BRCA1*, the relative risks of breast cancer were estimated to be 21.6 in women under 40 years of age, 9.6 in women 40–49 years of age, and 7.6 in women ≥50 years of age. On the basis of these estimates, the penetrance of breast cancer at age 70 among *BRCA1* mutation carriers is estimated to be 46% (95% confidence, 31%–80%) rising to 59% (95% confidence, 40%–93%) at age 80. For *BRCA2*, the relative risks in the same three age categories were estimated to be 3.3, 3.3, and 4.6, respectively, resulting in a penetrance at age 70 of 26% (95% confidence, 14%–50%) rising to 38% (95% confidence, 20%–68%) at age

80. The lifetime risk of breast cancer in Jewish women who are mutation carriers estimated via this approach is substantially lower than the reported lifetime risks estimated using multiple-case families. The risks appear to be different for carriers of *BRCA1* and *BRCA2* mutations.

Introduction

A number of studies have reported a high lifetime risk of breast cancer in carriers of *BRCA1* and *BRCA2* mutations identified through families with multiple occurrences of the disease (1–4). The Breast Cancer Linkage Consortium has conducted a series of such analyses as this resource of familial breast cancer has matured, leading to estimates of breast cancer penetrance at age 70 for *BRCA1* carriers in the range of 82% to 90% (1, 2), with a corresponding estimate of 84% for *BRCA2* (3). Similar estimates were obtained in these patients by evaluating the incidence of contralateral breast cancer (2, 4). However the use of cancer families for estimating penetrance is hampered by the fact that these families are ascertained on the basis of the identification of multiple occurrences of breast cancer. In fact, in the analyses of the Breast Cancer Linkage Consortium, families had to exhibit at least four cases of breast cancer at ages <60 years to be included. Because the occurrence of breast cancer in both individuals and families is, in part, a stochastic phenomenon, families that happen to exhibit several occurrences of breast cancer are more likely to be identified than families that exhibit few occurrences, even if their underlying risks are similar (5, 6). If risks are heterogeneous between families, then the higher-risk families will be preferentially selected. Consequently, the estimation of penetrance based on such families may lead to higher estimates than are applicable to mutation carriers in the population at large (7), notwithstanding the fact that the statistical models used to estimate penetrance endeavor to account for ascertainment bias (8).

In this study, we approached the problem of estimating penetrance using data that were designed to be representative of the population at large in an effort to eliminate any preferential selectivity of subjects on the basis of the occurrence of breast cancer in either the proband or any of the proband's relatives. We accomplished this by using cases of breast cancer and controls that are unselected on the basis of family history of breast cancer. Our data encompass three series of incident breast cancers in Jewish women in hospitals in New York and Canada. We then used the large series of volunteers from a community survey reported by Struwing *et al.* (9) in the Washington, D. C., area to permit estimation of the age-specific relative risks of breast cancer attributable to one of the three mutations that are relatively common in the Ashkenazi Jewish population, *i.e.*, 185delAG and 5382 insC in *BRCA1*, and 6174delT in *BRCA2*. Knowledge of these relative risks and of the age-specific prevalences of these mutations permits estimation of the age-specific incidence rates of breast cancer in

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mutation carriers, and from these the penetrance can be calculated directly. Thus our method does not rely at all on data on the familial aggregation of breast cancer. Our study builds upon the earlier study by Fodor *et al.* (10), which involved one of our three case series, and individuals referred for prenatal carrier testing as controls, leading to a lifetime penetrance estimate of 36% for a combined analysis of 185delAG and 6174delT carriers. In addition to the expanded case group and a different control group, our study uses age-specific cancer incidence rates and carrier prevalences to accomplish a more accurate statistical analysis.

In all of the individual studies, the women were self-identified as "Jewish," either from medical records in the case series or by responding to specific requests for recruitment of Jewish subjects, as in the volunteer study, where the vast majority of participants reported that they were Ashkenazi. In the hospital case series, the women were not specifically identified as being of Ashkenazi descent.

Materials and Methods

Cases. Cases were derived from studies conducted at Memorial Sloan-Kettering Cancer Center, New York, NY, the Mount Sinai Medical Center in New York, NY, and the Sir Mortimer B. Davis-Jewish General Hospital in Montreal, Canada. Results and case selection for each of these series has been reported previously (10–12). The series at Memorial Sloan-Kettering Cancer Center was assembled for the purpose of studying the clinical outcomes of carriers and noncarriers of *BRCA* mutations (11). Clinical records of all incident cases of breast cancer between 1980 and 1990 were reviewed. The study was limited to women who identified themselves as being Jewish at the time of hospital registration and to those who received breast-conserving therapy. Of the 393 women in this category, archival pathological material was available for 314. However, samples from nine patients failed to yield PCR products, and so the analysis is restricted to the remaining 305 patients. The study was performed in an anonymized manner in accordance with published guidelines regarding the conduct of genetic research on stored tissue samples (13). Thus, only limited information on patient factors is available, the most important for our purpose being age at diagnosis of breast cancer. All cases were analyzed for the presence of the breast cancer founder mutations common in individuals of Ashkenazi descent: *BRCA1* 185delAG, *BRCA1* 5382 insC, and *BRCA2* 6174delT. Additional details of the genetic analysis are described in the previous report of these patients (11).

Similar case ascertainment methods and genetic analyses were used in the other two series of patients with the exception that there was no restriction to patients receiving breast-conserving therapy. In the study at the Sir Mortimer B. Davis-Jewish General Hospital in Montreal, archival tissue from all self-identified Jewish patients with a first primary invasive breast cancer diagnosed between 1986 and 1995 was assembled for mutational analysis, excluding patients diagnosed after age 65. Breast cancer blocks were available from each of the 209 eligible women, and mutational analysis was successful for all cases, using methods described in more detail in Foulkes *et al.* (12). The study at Mount Sinai involved 298 self-identified Jewish women diagnosed with breast cancer between 1986 and 1995. After exclusions attributable to the absence of tissue blocks and a failure to obtain amplifiable DNA, the number of cases available for analysis is 268. Additional details of this study are provided by Fodor *et al.* (10). After aggregation of the data from all of these series, we obtain a total of 782 cases. Of

these, 71 (9%) were <40 years of age at diagnosis, 204 (26%) were between the ages of 40 and 49, and 507 (64%) were 50 years of age or older.

Controls. The study was facilitated by the availability of a large series of genotyped individuals without a history of breast or ovarian cancer obtained by Struewing *et al.* (9) in a volunteer study conducted in Washington, D. C. Jewish men and women were recruited through posters, newspapers, and radio announcements in the general and Jewish media. The subjects provided a blood sample for genetic analysis, and this was analyzed for the same three mutations described above. Some of these subjects were cancer survivors, and so we have restricted the control group to the 3434 women in the study who had no prior history of breast or ovarian cancer. This group contains 692 (20%) women <40 years of age, 1113 (32%) women between 40 and 49 years of age, and 1629 (47%) women 50 years of age or older. All analyses conducted are age-stratified, counterbalancing the problem that the age distribution of the controls reflects a substantially younger group than the cases.

Statistical Methods. The penetrance of breast cancer in gene carriers at a given age is the probability that a randomly selected carrier will develop breast cancer by that age, assuming that the individual does not die of other causes before that age (14). Thus, if we denote the age-specific incidence rates in carriers, expressed as probabilities, by I_1, I_2, \dots for age categories 1, 2, \dots then the penetrance at the end of the a^{th} age-interval is given by

$$P_a = 1 - [(1 - I_1)(1 - I_2)\dots(1 - I_a)]$$

To calculate P_a we need to know these age-specific incidence rates in carriers. The overall age-specific population incidence rates of breast cancer, denoted I_1^*, I_2^*, \dots , can be determined from cancer incidence registries. Furthermore, these rates are simply the weighted average of the rates in carriers and the rates in noncarriers, weighted by the age-specific prevalence of the mutation in the population. Consequently, the age-specific incidence rate in carriers can be expressed in terms of the population incidence rate, the gene prevalence and the age-specific relative risk of breast cancer in carriers as follows:

$$I_j = I_j^* \varphi_j / (\pi_j \varphi_j + 1 - \pi_j) \text{ for each age interval } j,$$

where π_j is the age-specific prevalence of the mutation and φ_j is the age-specific relative risk. Our analysis involves estimating these relative risks by determining the odds ratios from the cases and controls, estimating the prevalences using the controls, and by using the SEER² registry to determine the population incidence rates. This is similar in concept to the approach suggested by Gail *et al.* (15), with the exception that we are assuming that our controls are representative of the population base that is at risk of developing breast cancer, rather than a distinct nondiseased group from which cases are excluded. We note that, because the case-control comparisons are restricted to Jewish women, and the SEER data represent the entire population of the United States, the analysis is based on the assumption that the overall population incidence rates in Jewish women are similar to those of the general population. We performed some sensitivity analyses to address this issue. To obtain CIs for our penetrance estimate, we used the bootstrap

² The abbreviations used are: SEER, Surveillance, Epidemiology, and End Results; CI, confidence interval.

Table 1 Mutation rates in cases and controls

| Age (yr) | Institution | Mutation positive | 185delAG | 5382insC | 6174delT | Mutation negative | Total |
|----------|------------------------|-------------------|----------------|----------|----------------|-------------------|------------------|
| <40 | Memorial Hospital (NY) | 8 (29%) | 8 | 0 | 0 | 20 | 28 |
| | Mt. Sinai (NY) | 2 (13%) | 1 | 0 | 1 | 13 | 15 |
| | Montreal | 10 (36%) | 5 | 4 | 1 | 18 | 28 |
| | Controls | 19 (2.7%) | 9 | 2 | 8 | 673 | 692 |
| 40–49 | Memorial Hospital (NY) | 10 (15%) | 7 | 1 | 2 | 56 | 66 |
| | Mt. Sinai (NY) | 6 (7%) | 2 | 1 | 3 | 76 | 82 |
| | Montreal | 9 (16%) | 6 | 2 | 1 | 47 | 56 |
| | Controls | 23 (2.1%) | 9 | 3 | 11 | 1090 | 1113 |
| ≥50 | Memorial Hospital (NY) | 10 (5%) | 5 ^a | 1 | 5 ^a | 201 | 211 ^a |
| | Mt. Sinai (NY) | 10 (6%) | 5 | 1 | 4 | 161 | 171 |
| | Montreal | 14 (11%) | 6 | 2 | 6 | 111 | 125 |
| | Controls | 20 (1.2%) | 3 | 6 | 11 | 1609 | 1629 |

^a One patient was positive for both 185 del AG and 6174 del T.

Table 2 Case control analysis

| Age (yr) | Mutation status | Cases | Controls | Odds ratio ^a (95% confidence) |
|----------|-----------------|------------------------|-----------|---|
| <40 | BRCA1+ | 18 (25%) | 11 (1.6%) | 21.6 (9.7, 41.2) |
| | BRCA2+ | 2 (2.8%) | 8 (1.2%) | 3.3 (0.7, 15.9) |
| | Negative | 51 | 673 | |
| 40–49 | BRCA1+ | 19 (9.3%) | 12 (1.1%) | 9.6 (4.6, 20.2) |
| | BRCA2+ | 6 (2.9%) | 11 (0.9%) | 3.3 (1.2, 9.1) |
| | Negative | 179 | 1090 | |
| ≥50 | BRCA1+ | 20 ^b (3.9%) | 9 (0.6%) | 7.6 (3.4, 16.7) |
| | BRCA2+ | 15 ^b (3.0%) | 11 (0.7%) | 4.6 (2.1, 10.2) |
| | Negative | 473 | 1609 | |

^a Control group is subjects who are negative for both mutations.

^b One patient (at Memorial Hospital) was positive for both BRCA1 and BRCA2.

method (16). This involves recalculating the penetrance repeatedly using regenerated samples of cases and controls where the subjects are sampled with replacement, and using the distribution of these penetrance estimates to obtain the CIs.

Various additional tests were carried out using logistic regression to address the following issues. To formally evaluate the appropriateness of aggregating the three case groups, we evaluated the heterogeneity of the age-specific proportions of mutation carriers using an analysis, restricted to cases, in which the outcome was the mutational status. We then compared the model in which the effect of both age and the three geographic sites was included *versus* a model in which the geographic sites were excluded. Trend tests were performed to evaluate the impact of age on the odds ratios for each of the two genes separately by assessing the interaction between age and mutation status in a model with case/control status as the outcome. The hypotheses that the odds ratios conferred by *BRCA1* and *BRCA2* are equivalent, and that mutations in 185delAG and 5382 insC have equivalent impact, were tested using a model in which only gene carriers were analyzed, the outcome was the case/control status, and the included variables were mutation type (*BRCA1 versus BRCA2* or 185delAG *versus* 5382 insC), with age included to adjust for possible confounding. This model is technically equivalent to a polychotomous logistic regression model, but simpler to apply (17). For all of these analyses a likelihood ratio test was performed. Finally, we performed additional sensitivity analyses, first by altering the assumed underlying population incidence rates in the Jewish population, and second by eliminating individual case groups. The results of these sensitivity analyses are reported in the section entitled, "Discussion."

Results

The age-specific mutation rates in our three case series are set out in Table 1. These frequencies display some heterogeneity, and this is borne out by the logistic regression analysis described above, which indicates a significant degree of heterogeneity for *BRCA1* between the institutions ($P = 0.01$). This heterogeneity is apparent for both 185delAG ($P = 0.07$) and 5382 insC ($P = 0.03$). For *BRCA2*, there is no significant heterogeneity, although the low prevalences limit the statistical power for this comparison ($P = 0.60$). We elected to aggregate the data across the institutions in our primary analyses, because the magnitude of the heterogeneity appears relatively small, except for the unusually low frequency of *BRCA1* in the youngest age group at Mt. Sinai, and subsequently we reported a sensitivity analysis of this issue. We noted that the Memorial series involved only patients receiving breast-conserving surgery and thus eliminated patients with advanced disease at surgery; but there is no evidence from Table 1 that this exclusion had an impact because, for most of the configurations studied, the mutation prevalences from Memorial are intermediate between those of the other two series.

The aggregated mutation prevalences for *BRCA1* are 25% in the <40 age group, 9.3% in patients aged 40–49, and 3.9% in patients aged ≥50. These compare with prevalences of 1.6%, 1.1%, and 0.6%, respectively, in the control series (Table 2). We note that the reduction in prevalence among controls as the population ages is to be expected, because women who experience the disease are removed from the population at risk. Our estimates of the relative risks of breast cancer attributable to a *BRCA1* mutation are 21.6 in the <40 age group, 9.6 in subjects

Table 3 Penetrance analysis

| Age (yr) | SEER incidence rate ^a | Carrier prevalence | Relative risk | Carrier incidence rate | Penetrance (%) ^b (95% confidence) |
|--------------|----------------------------------|--------------------|---------------|------------------------|---|
| BRCA1 | | | | | |
| 20–29 | .0004 | .016 | 21.6 | 0.006 | 0.6% (0.3%, 1.5%) |
| 30–39 | .0040 | .016 | 21.6 | 0.065 | 7% (4%, 16%) |
| 40–49 | .0138 | .011 | 9.6 | 0.122 | 18% (12%, 34%) |
| 50–59 | .0212 | .006 | 7.6 | 0.155 | 31% (22%, 56%) |
| 60–69 | .0292 | .006 | 7.6 | 0.227 | 46% (31%, 80%) |
| 70–79 | .0342 | .006 | 7.6 | 0.249 | 59% (40%, 93%) |
| 80–89 | .0349 | .006 | 7.6 | 0.255 | 70% (47%, 98%) |
| BRCA2 | | | | | |
| 20–29 | .0004 | .012 | 3.3 | 0.001 | 0.1% (0.0%, 0.5%) |
| 30–39 | .0040 | .012 | 3.3 | 0.013 | 1.4% (0.0%, 5.4%) |
| 40–49 | .0138 | .010 | 3.3 | 0.045 | 6% (2%, 14%) |
| 50–59 | .0212 | .007 | 4.6 | 0.085 | 15% (8%, 28%) |
| 60–69 | .0292 | .007 | 4.6 | 0.117 | 26% (14%, 50%) |
| 70–79 | .0342 | .007 | 4.6 | 0.137 | 38% (20%, 68%) |
| 80–89 | .0349 | .007 | 4.6 | 0.140 | 47% (26%, 80%) |

^a Incidence rates are expressed as the probability of developing cancer over the relevant 10-year period. For example, for women aged 60–69, the SEER rate is 292 per 100,000 person-years, which is equivalent to a probability of 0.0292 for an individual woman over this 10-year age range.

^b Probability of a carrier developing cancer by the end of the age interval.

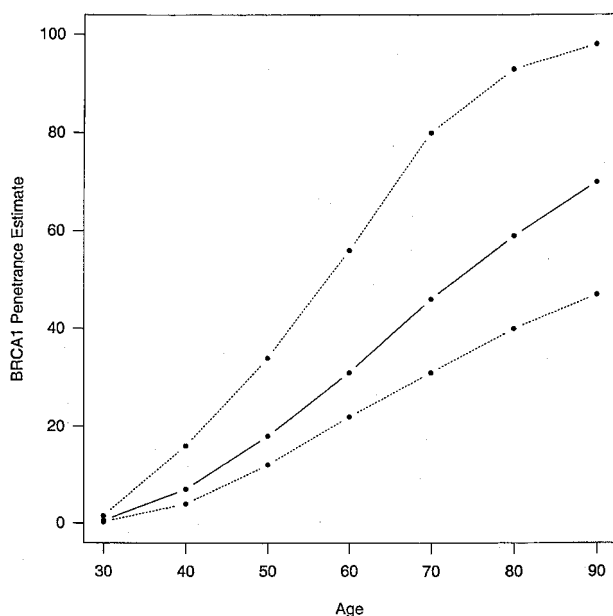


Fig. 1. Penetrance of *BRCA1* by age (solid curve); 95% CIs (dashed curves).

aged 40–49, and 7.6 in subjects more than 50 years of age or older ($P = 0.04$; trend test). Using these data and the formula defined in “Materials and Methods,” we obtained the age-specific incidence rates in carriers (Table 3, top, column 5), and the corresponding penetrance function (Table 3, column 6, and Fig. 1). Our estimate of the penetrance at age 70 is 46% [95% CI, 31%–80%]. We have repeated these analyses for *BRCA2* mutations (Table 3 and Fig. 2). The results show that *BRCA2* is a much weaker risk factor, with relative risks of 3.3, 3.3, and 4.6 in the three age groups, resulting in a penetrance at age 70 of 26% [95% CI, 14%–50%]. Our analysis also shows that the risk induced by *BRCA1* is significantly greater than that conferred by *BRCA2* ($P = 0.01$).

We have repeated the penetrance analyses separately for

the two *BRCA1* mutations, recognizing that the low frequency of 5382 insC prohibits a reliable analysis. The resulting penetrance estimates at age 70 are 75% (95% CI, 43%–100%) for 185delAG and 29% (95% CI, 13%–69%) for 5382 insC, a difference that is not statistically significant despite the large difference in magnitude ($P = 0.14$).

Because the Montreal case series had an age cutoff of 65 years, we repeated all of the preceding analyses with an additional age stratification at age 65. The results were essentially unchanged, with the penetrance estimate at age 70 for *BRCA1* increasing by 1% to 47%, and the corresponding estimate for *BRCA2* decreasing by 1% to 25%.

Discussion

With the exception of the study by Fodor *et al.* (10), upon which this study is built, previous estimates of the penetrance of breast cancer have all relied on family data in one way or another. Early studies obtained the estimate using non-genotyped incident breast cancer cases and the techniques of segregation analysis, such as the study by Claus *et al.* (18), which led to a lifetime risk of 69%, and the study by Whittemore *et al.* (19), using cases of ovarian cancer from a previous case-control study, which also led to a penetrance estimate of 69%. Other studies have used the family history of probands of gene carriers, notably the studies by the Breast Cancer Linkage Consortium, which have produced estimates of penetrance at age 70 in the range of 85% for *BRCA1* (2) and 84% for *BRCA2* (4). Lower estimates have been obtained using analogous methods when the probands have been unselected on the basis of family history, notably the study by Struwing *et al.* (7, 9), which led to an estimate of 56% for the combination of the two genes, and recent studies by Warner *et al.* (20) that reported estimates of 60% for *BRCA1* and 28% for *BRCA2*, Antoniou *et al.* (21) that reported an estimate of 45% for *BRCA1* using families of a population-based series of ovarian cancer probands, and Hopper *et al.* (22), in Australia, that reported estimates of 36–40% in a combined analysis of the two genes.

The estimates in our study, 46% and 26% at age 70 in *BRCA1* and *BRCA2* carriers, respectively, are among the lowest of the estimates obtained thus far. The novelty of our approach is that, not only do we use probands who are unselected on the

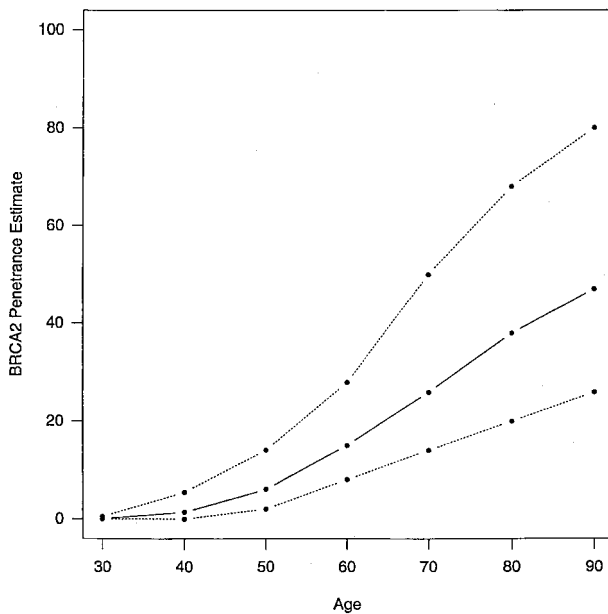


Fig. 2. Penetrance of *BRCA2* by age (solid curve); 95% CIs (dashed curves).

basis of family history, we do not use family history data at all. We rely solely on the comparison of the mutation frequencies in the unselected cases and controls, and the known population age-specific rates of breast cancer to estimate the penetrance directly. Our study is opportunistic in that we have taken advantage of the availability of various genotyped case series, a large group of genotyped controls, and by the fact that the three mutations under investigation are known to have a high prevalence among Jews.

Our study aggregates data from two different populations. The odds ratio estimates are derived from the Jewish population, and thus the mutations studied are limited to the three mutations common in this population. The underlying incidence rates, from SEER, reflect the general population of the USA. Thus, our penetrance estimates apply to the population of Jewish women and are based on the assumption that the overall population incidence rates of breast cancer in Jewish women are similar to those of the United States as a whole. In fact, there is a paucity of epidemiological evidence regarding the comparability of incidence rates in Jewish and non-Jewish women. In their review of breast cancer risk factors, Kelsey and Horn-Ross (23) suggested that Jewish women are at elevated risk, and the relative risk was reported to be 1.1 in a recent case-control study (24). By contrast, the incidence rate of breast cancer is lower in Israel than in the United States (23). All of the study participants, both cases and controls, came from regions of the Northeast, where breast cancer rates are known to be higher than the national average. However, even if we recalculate the penetrances by assuming that the risk of breast cancer in Jewish women is 10% higher than the national rates, these recalculated penetrances at age 70 only increase to 49% and 29% for *BRCA1* and *BRCA2*, respectively. If we perform this recalculation assuming that the rates in Jewish women are actually 20% higher than the national rates, then the penetrance estimates increase to 53% and 31%, respectively. These sensitivity analyses indicate that our conclusions about the magnitudes of the penetrances are not markedly affected by our assumptions about the underlying breast cancer incidence rates in Jews.

A prominent limitation of the study is the fact that the comparison group was not selected in a random population-based manner. In fact we must assume that the carrier frequencies in the control group, obtained in a volunteer fashion in the Washington, D. C. area, are the same as those of the population of Jewish women in the regions of New York and Montreal, which comprise the population base for the incident breast cancer cases in the study hospitals (25). The volunteer survey was, in fact, assembled through public advertisements. Thus, women with a family history of breast cancer may have been more likely to volunteer, and, indeed, the investigators reported data to suggest an elevated frequency of breast cancer family history (9). However, the overall mutation prevalence reported in this study in women with no prior breast or ovarian cancer is comparable with two other reported control groups of young Jewish women who were assembled for prenatal testing (10) and general screening for Jewish genetic diseases (26). In these studies of generally younger subjects (the ages are unknown because of anonymization issues), the mutation prevalences (*BRCA1* and *BRCA2* combined) were reported as 2.2% and 2.7%, respectively. In the control group that we used, the overall prevalence was 1.8%, and it was 2.8% in the <40 age group. Thus, there is no apparent evidence that the control mutation prevalences are artificially high, which would result in underestimation of the penetrance. Our estimates of the mutation prevalences in controls are, however, slightly underestimated for the technical reason that we elected to present the calculations in Table 3 in 10-year, age-specific intervals for ease of interpretation, thereby implicitly eliminating from the control group individuals who would have developed cancer during the relevant age-range. Estimating the penetrance using much smaller age intervals to eliminate the impact of this problem lowers the estimates of penetrance by 2% for *BRCA1* and by 1% for *BRCA2*.

The three case series have the disadvantage of being hospital-based and also geographically idiosyncratic. It is curious that there seems to be some heterogeneity in mutation prevalence, with the series at Mt. Sinai Hospital exhibiting generally lower prevalences than the two other series, especially in the younger age groups (Table 1). This may reflect true differences in prevalence in the populations that attend these hospitals, or it may be simply a statistical artifact. However, we repeated our analyses excluding the Mt. Sinai series, and the resulting estimates of penetrance at age 70 increased only from 46% to 51% for *BRCA1* and from 26% to 27% for *BRCA2*.

We recognize that, despite the large numbers of women represented in this study, the CIs for our penetrance estimates remain quite wide. Indeed, the upper 95% interval for *BRCA1* penetrance at age 70, 80%, is close to the estimate of 85% from the studies of the Breast Cancer Linkage Consortium. The reason for this limited precision is the rarity of these germ-line mutations, and this makes the study of the impact of these mutations using conventional epidemiological techniques especially challenging. By focusing on the Jewish population and its known founder mutations with relatively high prevalence, on the order of 2% in controls, we have succeeded in creating the conditions for a study that can feasibly provide a direct estimate of penetrance.

Despite these reservations, we believe that the study contributes to the evidence that penetrance in mutation carriers is lower than the estimates obtained from studies of high-risk families. Because penetrance is determined by the age-specific incidence rates in carriers, the most direct and methodologically credible way to estimate penetrance would be to measure incidence rates from cohorts of carriers unselected on the basis of

a cancer outcome. Because prospective cohort studies of high-risk populations without preventive intervention are not practical, alternative approaches are justified. In the current study, age-specific relative risks are estimated by comparing unselected cases and controls, all of which were genotyped, in the manner of a case-control study, and incidence rates were imputed from these estimates. Because hospital incident cases and volunteer controls were used, it is not the ideal case-control study for the reasons discussed above. However, the relative similarity of the carrier prevalences in the three case series, and also in the various control groups cited, provide reassurance that the estimates are broadly reliable.

The prevalences of *BRCA* mutations seem to be substantially higher in those of Ashkenazi background than in unselected American women (19, 27) or in Chinese women (28). Like the mutations seen in the Ashkenazim, most disease-causing *BRCA1* and *BRCA2* mutations in other populations are predicted to result in a nonfunctional truncated protein product. However, early studies of genotype-phenotype correlations of both *BRCA1* and *BRCA2* mutations have suggested variation in both the clinical characteristics of diagnosed cancers (29) and the risks of these cancers (30). Therefore, the applicability of the results of the current study to populations of other ethnic ancestry is a matter of conjecture at this time; but it is notable that a recent study of founder *BRCA2* mutation in Iceland using the kin-cohort methodology produced a penetrance estimate of 37% at age 70, as compared with our estimate of 26% (31). We note that we have elected in our presentations to emphasize the results of our separate analyses of the penetrance of *BRCA1* and *BRCA2*, while emphasizing our aggregated analysis of the two *BRCA1* mutations, despite the fact that our individual analyses of 185delAG and 5382 insC led to strikingly different estimates of penetrance. This emphasis is a matter of judgment based on the relatively small frequencies of 5382 insC and the fact that the aggregated mutations occur on the same gene. In fact, heterogeneity of the effects of different mutations on the same gene, if it exists, can only be determined reliably by larger studies of this nature.

The risk estimates of 46% and 26% by age 70 for *BRCA1* and *BRCA2*, respectively, in the current study are among the lowest yet reported in a large series. These lower estimates may have an impact on counseling (32–34). However, at the present time, it remains unclear as to the range of variation of penetrance functions between families. Differences in penetrance estimates in prior studies may have been a result of bias attributable to ascertainment. However, it is also possible that other genetic or environmental (e.g., hormonal) factors may modify penetrance in different kindreds. In fact, a recent case-control study restricted to *BRCA* carriers demonstrated a significant effect of pregnancy on risk (35). Additional studies are needed to measure the impact of these genetic and epidemiological variables on risk for hereditary breast cancer in unselected series.

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