Published in final edited form as:

J Clin Oncol. 2006 February 20; 24(6): 863–871.

Characterization of *BRCA1* and *BRCA2* Mutations in a Large United States Sample

Sining Chen, Edwin S. Iversen, Tara Friebe, Dianne Finkelstein, Barbara L. Weber, Andrea Eisen, Leif E. Peterson, Joellen M. Schildkraut, Claudine Isaacs, Beth N. Peshkin, Camille Corio, Leoni Leondaridis, Gail Tomlinson, Debra Dutson, Rich Kerber, Christopher I. Amos, Louise C. Strong, Donald A. Berry, David M. Euhus, and Giovanni Parmigiani

From the Departments of Environmental Health Sciences and Biostatistics, Johns Hopkins Bloomberg School of Public Health; The Sidney Kimmel Comprehensive Cancer Center and the Department of Biostatistics, Johns Hopkins University, Baltimore, MD; Departments of Biostatistics and Bioinformatics and Community and Family Medicine, Duke University, Durham, NC; Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, PA; The Massachusetts General Hospital, Boston, MA; Translational Medicine and Genetics, GlaxoSmithKline, West Chester, PA; Preventive Oncology and Medical Oncologist, Toronto Sunnybrook Regional Cancer Centre, Toronto, Ontario, Canada; Departments of Medicine and Molecular and Human Genetics, Baylor College of Medicine; Departments of Epidemiology, Molecular Genetics, and Biostatistics, University of Texas M.D. Anderson Cancer Center, Houston; Departments of Pediatrics and Surgery, University of Texas Southwestern, Dallas, TX; Georgetown University Lombardi Cancer Center, Washington, DC; and Huntsman Cancer Center, University of Utah, Salt Lake City, UT

Abstract

Purpose—An accurate evaluation of the penetrance of *BRCA1* and *BRCA2* mutations is essential to the identification and clinical management of families at high risk of breast and ovarian cancer. Existing studies have focused on Ashkenazi Jews (AJ) or on families from outside the United States. In this article, we consider the US population using the largest US-based cohort to date of both AJ and non-AJ families.

Methods—We collected 676 AJ families and 1,272 families of other ethnicities through the Cancer Genetics Network. Two hundred eighty-two AJ families were population based, whereas the remainder was collected through counseling clinics. We used a retrospective likelihood approach to

Address reprint requests to Sining Chen, MD, Johns Hopkins Bloomberg School of Public Health, 615 N Wolfe St, W7041, Baltimore, MD 21205; e-mail: sichen@jhsph.edu.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

Author Contributions

Conception and design: Sining Chen, Edwin S. Iversen, Tara Friebe, Dianne Finkelstein, Barbara L. Weber, Andrea Eisen, Leif E. Peterson, Joellen M. Schildkraut, Claudine Isaacs, Beth N. Peshkin, Camille Corio, Leoni Leondaridis, Gail Tomlinson, Debra Dutson, Rich Kerber, Christopher I. Amos, Louise C. Strong, Donald A. Berry, David M. Euhus, Giovanni Parmigiani

Financial support: Giovanni Parmigiani

Collection and assembly of data: Tara Friebe, Dianne Finkelstein, Barbara L. Weber, Andrea Eisen, Leif E. Peterson, Joellen M. Schildkraut, Claudine Isaacs, Beth N. Peshkin, Camille Corio, Leoni Leondaridis, Gail Tomlinson, Debra Dutson, Rich Kerber, Christopher I. Amos, Louise C. Strong, Donald A. Berry, David M. Euhus

Data analysis and interpretation: Sining Chen, Edwin S. Iversen, Giovanni Parmigiani

Manuscript writing: Sining Chen, Edwin S. Iversen, Giovanni Parmigiani

Final approval of manuscript: Sining Chen, Edwin S. Iversen, Tara Friebe, Dianne Finkelstein, Barbara L. Weber, Andrea Eisen, Leif E. Peterson, Joellen M. Schildkraut, Claudine Isaacs, Beth N. Peshkin, Camille Corio, Leoni Leondaridis, Gail Tomlinson, Debra Dutson, Rich Kerber, Christopher I. Amos, Louise C. Strong, Donald A. Berry, David M. Euhus, Giovanni Parmigiani

correct for bias induced by oversampling of participants with a positive family history. Our approach takes full advantage of detailed family history information and the Mendelian transmission of mutated alleles in the family.

Results—In the US population, the estimated cumulative breast cancer risk at age 70 years was 0.46 (95% CI, 0.39 to 0.54) in *BRCA1* carriers and 0.43 (95% CI, 0.36 to 0.51) in *BRCA2* carriers, whereas ovarian cancer risk was 0.39 (95% CI, 0.30 to 0.50) in *BRCA1* carriers and 0.22 (95% CI, 0.14 to 0.32) in *BRCA2* carriers. We also reported the prospective risks of developing cancer for cancer-free carriers in 10-year age intervals. We noted a rapid decrease in the relative risk of breast cancer with age and derived its implication for genetic counseling.

Conclusion—The penetrance of *BRCA* mutations in the United States is largely consistent with previous studies on Western populations given the large CIs on existing estimates. However, the absolute cumulative risks are on the lower end of the spectrum.

INTRODUCTION

Germline deleterious mutations in the *BRCA1* (MIM 113705) and *BRCA2* (MIM 600185) genes convey a significantly elevated risk of developing breast and ovarian cancer and of developing these cancers at earlier ages. Such mutations are considered to be responsible for approximately 40% of familial breast cancer and for the majority of familial ovarian cancers^{1–3} and account for 5% to 20% of the total percentage of breast and ovarian cancers.^{4–6} The screening, counseling, testing, and clinical management of families at high risk for these mutations relies on an accurate characterization of the *BRCA1* and *BRCA2* genes and particularly on the evaluation of the penetrance (the risk of developing cancer in carriers) and prevalence of mutations in these genes.^{7–9}

Earlier studies from the Breast Cancer Linkage Consortium were conducted on families with four or more members having cancer.^{10–13} These studies reported a breast cancer risk of approximately 80% at age 70 years for mutation carriers. There is a potential for these estimates to be biased upwards because of the use of a logarithm of the odds (LOD) score-maximization approach while ascertaining families with high LOD scores. Later studies have focused attention on population-based samples or case-series cohorts.^{14–18} Struwing et al¹⁴ led a population-based study that obtained participants through Ashkenazi Jewish (AJ) volunteers in the Washington, DC, area. Hopper et al¹⁵ estimated breast cancer risk for carriers of a predefined set of mutations through early-onset patients from a population-based Australian cancer registry. Satagopan et al^{16,19} conducted two New York hospital-based case-control studies that estimated breast and ovarian cancer risks from AJ patients. Antoniou et al¹⁷ assembled information from 22 studies that were based on unselected index cases (ie, the family was ascertained through an individual with breast or ovarian cancer, who was sampled independently of family history). This also included data from the United Kingdom-based Anglian Breast Cancer Study.²⁰ More recently, King et al¹⁸ derived penetrance by genotyping 1,008 New York hospital-based female AJ breast cancer patients and all of their female relatives. Risk estimates from these studies have a broad range. For example, Hopper et al¹⁵ found a cumulative breast cancer risk for *BRCA1* or *BRCA2* carriers at age 70 years of 36%, whereas King et al¹⁸ reported a risk of 71%.

To obtain a sufficient number of carriers with such population-based designs, studies are usually carried out on sub-populations that segregate founder mutations at higher frequencies, such as the AJ population. In the general population, where mutation prevalence is approximately 10% of that in AJs, it would be much more costly to arrive at estimates with similar precision using population-based designs.

In this article, we study the largest set to date of detailed family histories from US families, including both AJ and non-AJ families, and provide estimates of breast and ovarian cancer risk in *BRCA1* and *BRCA2* mutation carriers. Families were assembled through the National Cancer Institute's Cancer Genetics Network (CGN) in eight centers across the United States.

METHODS

Families

Using the CGN, we created a multicenter database for the study of the *BRCA* genes in the US population. Eight centers within the CGN (Table 1) provided detailed family history information. There are a total of 1,948 families in the database. Of these, 676 are AJs, and 1,272 are not. Most families were acquired through high-risk counseling clinics. Although criteria for inclusion varied across centers, most families have a positive family history of breast or ovarian cancer. On average, there were more than three diagnoses of breast or ovarian cancer per family. As an exception to the retrospective family history-based sampling scheme, the 282 AJ families recruited by the Baylor College of Medicine were population based.

Family history information included whether the family was of AJ origin and, for the counselee and his or her first- and second-degree relatives, the following variables: affection status (cancer of breasts and/or ovaries), age at onset if affected, and age of last follow-up or death if not affected. For each family, genetic test results were reported to us for one individual, who was called the counselee. Table 2 lists the characteristics of the counselees.

Mutation Analysis

Mutation analysis had been previously performed on all 1,948 counselees on one or both of the genes. A total of 283 *BRCA1* mutations carriers and 143 *BRCA2* mutations carriers were identified. An array of testing techniques were used, including direct sequencing, targeted sequencing for AJ founder mutations, allele-specific oligohybridization, denaturing gradient gel electrophoresis, denaturing high-pressure liquid chromatography, and protein truncation test. The number of families tested with each technique or combination of techniques are listed in Table 3. Because different germline testing techniques have different sensitivities, we accounted for mutation analysis errors using the sensitivity estimates listed in Table 3. We discuss in the Appendix how those estimates were derived and used.

Statistical Methods

We use a Mendelian retrospective likelihood approach^{21,22} that takes advantage of all available family history information while correcting for ascertainment bias from oversampling families with multiple patients. This is similar in spirit to the maximum LOD score approach, whereas the likelihood considers joint estimation of the risk of breast and ovarian cancers in both *BRCA1* and *BRCA2* carriers as well as relative prevalence parameters.

Penetrance Definition and Parameterization

In this article, we define penetrance to be the genotype-specific, age-specific cumulative probability of developing a cancer at a specific site for the first time, removing death and other competing risks. To model the different age distribution of cancer onset in carriers and noncarriers, we use a relative risk (RR) parameterization. The hazard of developing cancer at age t for mutation carriers [$h_c(t)$] is equal to the hazard for noncarriers [$h_n(t)$] times the RR at that age [$RR(t)$]. That is:

$$h_c(t) = h_n(t) \times RR(t)$$

In turn, the relative risk $RR(.)$ is estimated by the 10-year age intervals of 20 to 29, 30 to 39, 40 to 49, 50 to 59, and 60 to 69 and is assumed to be constant within those age intervals. The RR is not estimated for the age interval of 20 to 29 for ovarian cancer because there are too few patients in that age interval. As the hazard of breast or ovarian cancer in noncarriers, we use the Surveillance, Epidemiology, and End Results age-conditional probabilities of developing cancer.²³ The Surveillance, Epidemiology and End Results program publishes authoritative and comprehensive cancer incidence data from 11 population-based registries throughout the United States.²⁴ We use the population-based hazard as the noncarrier hazard because mutations are sufficiently rare (< 2 carriers per 1,000). The age-conditional probability is the probability of developing cancer given that a person is alive and cancer free at that age. This serves as the appropriate baseline for our hazard of interest.

Prospective and Retrospective Likelihood Components

Our estimation is based on a likelihood function for the penetrance parameters, ϕ and prevalence parameter π . Each individual contributes differently to the likelihood function depending on how the data about him or her were collected. For a prospectively collected individual (ie, the 282 families from Baylor College of Medicine), we use the prospective likelihood, as follows:

$$P(F, T | \phi, \pi) \quad (1)$$

which is the probability of the family history (F) and the genetic test result (T) given the penetrance and prevalence. For the retrospectively collected, or high-risk, individuals, we write the retrospective likelihood, as follows:

$$P(T | F, \phi, \pi) \quad (2)$$

which is the probability of the genetic test result given the family history and penetrance and prevalence. This allows us to account for the fact that the family is collected based on its family history F and leads to an unbiased estimate of the penetrance in the presence of heterogeneous and uncertain mechanisms of family ascertainment.^{21,25,26}

Allele Frequencies

The population prevalence of mutations π is important in calculating a Mendelian likelihood (see Appendix). It can also be expressed in terms of the allele frequency f ($\pi = 2f - f^2$). The frequencies of the three AJ founder mutations have been well estimated by several large population-based studies.^{14,27–29} These studies provided similar estimates; a meta-analysis of these studies²² gives allele frequencies of 0.0061 and 0.0068 on *BRCA1* and *BRCA2*, respectively. In our analysis, we fix the combined allele frequency on both genes at 0.0129, while allowing the ratio of mutation frequency of *BRCA1* to *BRCA2* to be estimated from the data.

The allele frequencies in the non-AJ population have been studied using case-series data or multiple-patient families. Ford et al¹³ gave a 95% CI of 0.0002 to 0.0010 in *BRCA1*; Andersen³⁰ estimated *BRCA2* mutated allele frequency at 0.0002; and Antoniou et al³¹ used segregation analysis to arrive at 0.00042 for *BRCA1* and 0.00054 for *BRCA2* under the major genes model, although estimates are slightly different under different models. We fixed the combined allele mutation frequency at 0.0008, which is the current default of the genetic counseling software BRCAPRO,²² whereas we estimated the proportion of *BRCA1* mutations.

Statistical Computing

We estimated the model parameters using a Monte Carlo Markov Chain method. The estimates are reported in the form of a posterior mean and the corresponding posterior 95% probability interval. Uniform or noninformative priors were used throughout.

Genetic Counseling Implications: Bayes Factor

At a genetic counseling clinic, the counselee is provided with his or her odds of being a carrier given his or her family history information, which s/he can use to make decisions about genetic testing and to evaluate cancer risk. These odds can be calculated as the Bayes factor (BF) multiplied by the prior odds, as follows:

$$\begin{aligned}\text{Odds} &= \frac{\Pr(\text{carrier})|\Pr(\text{family history})}{\Pr(\text{noncarrier})|\Pr(\text{family history})} \\ &= \frac{\Pr(\text{family history}|\text{carrier})}{\Pr(\text{family history}|\text{noncarrier})} \times \frac{\Pr(\text{carrier})}{\Pr(\text{noncarrier})} \\ &= \text{BF} \times \text{Prior Odds}\end{aligned}\quad (3)$$

The BF is defined as the ratio of the probability of the family history given that the counselee carries a mutation versus no mutation. It measures the evidence provided by the family history towards the counselee carrying a mutation, and it is a crucial quantity in genetic counseling practice because it permits one to mathematically translate a complex family history into a summary that is of direct relevance to decision making.

The other key element is the prior odds. These reflect the mutation prevalence, which, however, affects only weakly the BF. Thus, the same family history may yield a BF of approximately 50 for counselees in both AJ and non-AJ families. Although this is strong evidence towards a mutation in both types of counselees, the resulting carrier probability is 0.57 for the AJ counselee and 0.07 for the non-AJ counselee. This difference is a result of the different mutation prevalence, although the severity of family history is the same.

To illustrate the implications of penetrance in calculating the BF, we present the case in which the counselee seeks genetic counseling immediately after being diagnosed with cancer and is not aware of the disease history of any relatives. The BF in this case is as follows:

$$\text{BF} = \frac{\Pr(\text{cancer at age } t|\text{carrier})}{\Pr(\text{cancer at age } t|\text{noncarrier})}\quad (4)$$

To counsel a person with a family history, we derive the BF based on her particular family history. For a simple example, a healthy counselee whose mother had a breast cancer diagnosis at age 35 years would be calculated as follows:

$$\text{BF} = \frac{\Pr(\text{mother breast cancer at 35, daughter healthy at 20}|\text{daughter is carrier})}{\Pr(\text{mother breast cancer at 35, daughter healthy at 20}|\text{daughter is noncarrier})}\quad (5)$$

The numerator can be evaluated using penetrance estimates by decomposing it as follows:

$$\begin{aligned}&\Pr(\text{mother breast cancer at 35, daughter healthy at 20}|\text{mother carrier, daughter carrier}) \\ &\times \Pr(\text{mother carrier}|\text{daughter carrier}) + \\ &\Pr(\text{mother breast cancer at 35, daughter healthy at 20}|\text{mother noncarrier, daughter carrier}) \\ &\times \Pr(\text{mother noncarrier}|\text{daughter carrier})\end{aligned}\quad (6)$$

Both terms in the summation are products of one factor involving penetrance and another factor involving well-understood Mendelian genotype calculations. The denominator can be evaluated similarly. Please refer to the Appendix and other publications^{32–34} for additional details and examples.

The BF is different from the RR in that it is a ratio of densities and not hazards. The relationship between BF and RR can be expressed as follows:

$$\begin{aligned} \text{BF} &= \frac{\Pr(\text{cancer at age } t | \text{cancer free at } t-1, \text{ carrier})}{\Pr(\text{cancer at age } t | \text{cancer free at } t-1, \text{ noncarrier})} \\ &\quad \times \frac{\Pr(\text{cancer free at } t-1 | \text{carrier})}{\Pr(\text{cancer free at } t-1 | \text{noncarrier})} \\ &= \text{RR} \times \frac{\Pr(\text{cancer free at } t-1 | \text{carrier})}{\Pr(\text{cancer free at } t-1 | \text{noncarrier})} \end{aligned} \quad (7)$$

Because carriers develop cancer at a higher rate than noncarriers in early years, at any subsequent age, the proportion of carriers who have yet to develop cancer is less than the proportion of noncarriers who have yet to develop cancer. Thus, the ratio

$$\frac{\Pr(\text{cancer free at } t-1 | \text{carrier})}{\Pr(\text{cancer free at } t-1 | \text{noncarrier})} \quad (8)$$

is smaller than 1. This implies that, theoretically, a BF can be smaller than 1 when the RR is greater than 1 when the carriers develop cancer faster early on so that there are fewer of them remaining cancer free in the older population.

RESULTS

The age-specific cumulative risks, or penetrances, are listed in Table 4. The estimated breast cancer penetrances at age 70 years were 0.46 (95% CI, 0.39 to 0.54) in *BRCA1* carriers and 0.43 (95% CI, 0.36 to 0.51) in *BRCA2* carriers, whereas ovarian cancer penetrances at age 70 years were 0.39 (95% CI, 0.30 to 0.50) in *BRCA1* carriers and 0.22 (95% CI, 0.14 to 0.32) in *BRCA2* carriers. Cancer risks were close to those reported on an Italian population,³⁵ similar to those reported by Satagopan et al¹⁶ and Antoniou et al,¹⁷ and generally consistent with most past findings given the statistical variances reported. Our study suggests lower absolute ovarian cancer risks among *BRCA2* mutation carriers than among *BRCA1* mutation carriers. This finding is consistent with other studies.^{17–19,35}

At genetic counseling clinics, it is important to assess the future cancer risks for a cancer-free counselee. We report such risks Figure 1 and Table 5. Risks and associated CIs are provided for every 10-year interval from age 20 to 70 years. A counselee can directly read her prospective risks from one of the curves in this figure and from one row of the table depending on her current age and use them to make clinical decisions such as for prophylactic surgeries.

Table 6 and Figure 2 report our relative risk estimates. For breast cancer, the RRs were high in early ages and rapidly decreased. This trend is confirmed by Antoniou et al¹⁷ and partially confirmed by Satagopan et al.¹⁶ However, our reported RR was much higher in the 20- to 29-year-old age group, and the decreasing trend was steeper. The availability of a large number of families in our sample has allowed us to estimate this RR more precisely than other studies. For ovarian cancer, RRs were consistently high across age groups and did not have a clear increasing or decreasing trend. The RRs for *BRCA2* carriers were lower than for *BRCA1* carriers. This is consistent with Satagopan et al¹⁹ and Antoniou et al.¹⁷ There were too few participants of ages 20 to 29 to precisely estimate risk for that age interval.

In Table 7, we reported the Bayes Factor (BF), or the ratio of the age-specific risks, as evidence towards carrying a mutation given a diagnosis at various ages. By comparing Table 6 with Table 7, we see that the BF is smaller than the RR and increasingly so at higher ages. For breast cancer at age interval 60 to 69 years, the BFs are not distinguishable from 1. This has significant implications for genetic counseling and for current practices in selecting high-risk individuals and families.

In our penetrance estimation, we pooled the AJ and non-AJ families. We also carried out separate analyses for these two subgroups. The two sets of results were close to each other at both cancer sites and all age intervals; none of the differences was close to being statistically significant. The only other study with both AJ and non-AJ participants^{17,36} also did not notice a significant difference in penetrance between the two groups. Without strong evidence of a difference, we can achieve better accuracy by pooling the two groups. As expected, the result of the pooled analysis is similar to both sets of estimates from the separate analyses, with improved accuracy.

DISCUSSION

In this article, we provided an analysis of the largest US collection of both AJ and non-AJ families who have been ascertained for mutation analysis of *BRCA1* and *BRCA2*. Because of our large sample size, the estimates that we provide are more accurate than those provided by previous studies.

Several findings have direct impact on counseling and screening. First, our study reported the future risks of developing cancer for cancer-free mutation carriers. Risks given in this form can be immediately used by a genotyped individual to make preventative decisions for herself and her relatives. They can also be used in establishing cancer screening recommendations at various ages for mutation carriers.

Second, our study found the RRs and BFs of breast cancer to be high in early ages, and then they rapidly decrease. This decreasing trend is the result of both a decreasing risk for carriers and an increasing risk for noncarriers. It is widely believed and used informally in genetic counseling practice that early-onset breast cancers are a strong indicator for germline mutations. Our study provided concrete quantitative evidence for this hypothesis. The high BFs that we obtained for the age groups from 20 to 49 years clearly indicate the importance of considering mutation analysis in counselees presenting with breast cancer in this age range. In the age interval of 60 to 69 years, the BF for breast cancer cases decreased to nearly 1, suggesting only weak evidence in favor of a mutation for women diagnosed with cancer in this age range.

Last, we found consistently high RRs and high BFs for ovarian cancer for all ages. This is in accordance with the literature and empirical observation that the presence of any ovarian cancer diagnosis is strong evidence towards an inherited mutation, regardless of the age of diagnosis.
11

Prophylactic oophorectomy is widely accepted as a risk reduction procedure in women who are found to be *BRCA1/2* mutation carriers. Bilateral prophylactic oophorectomy (BPO) is reported to cut the risk of ovarian cancer by 96% (95% CI, 84% to 99%) and the risk to breast cancer by 53% (95% CI, 23% to 71%) among carriers.³⁷ In the CGN centers, 27% to more than 60% of unaffected women who received a positive mutation analysis result underwent prophylactic oophorectomy within a year after the mutation testing^{38,39}; this includes centers where all carrier women received a BPO unless they were less than 30 years old and/or had a desire to have children. By combining the results of our study and the risk reduction estimates

just given, we derived the future risks for an asymptomatic woman who underwent BPO, which are reported in Table 8.

Ignoring the status of BPO leads to the underestimation of penetrance in prospective studies.⁴⁰ However, this is unlikely to affect our analysis because, at the time the family history was collected, the probands and their relatives had not yet been genotyped. The rate of oophorectomy is only high for those women who are known carriers; the rate is low among women who do not yet know their genotype.⁴¹

Although our study includes mostly families having a strong history of breast or ovarian cancer, by using a retrospective likelihood, we can appropriately account for this sampling design, and in fact, we obtain penetrance estimates that are similar to those obtained from population-based designs. In addition, this approach allows more powerful estimates for probabilities of events that are rare in population-based samples, such as early-onset breast cancers. With the use of a Mendelian likelihood, we take advantage of all biologic information in the family history and are able to obtain penetrance estimates with tight CIs. A limitation of the likelihood formulation that we used is the lack of a parameter to model residual genetic or familial factors beyond the risks conferred by *BRCA1* or *BRCA2*. If these factors have a strong impact on familial risk of cancer, it is possible that our model could overestimate absolute risks for cancer as a result of *BRCA1* or *BRCA2*. However, King et al¹⁸ suggested that heterogeneity in the penetrance among *BRCA1/2* carriers is unlikely to be significant.

We conducted a sensitivity analysis examining how our estimates change if we use different assumptions on the combined allele frequency of *BRCA1* and *BRCA2* deleterious variants. The combined frequency is strongly negatively correlated with breast cancer risk for *BRCA1* mutation carriers.

Our statistical methodology has taken extensive care in accounting for family ascertainment issues, site heterogeneity, and sensitivities of mutation analysis techniques (see Appendix). Yet, because of the scope and computational complexity of the project, some simplifying assumptions had to be made. An important one is that testing results are conditionally independent of the family history and other parameters given the genotype. This could be violated in practice if there are additional sources of familial aggregation.^{42,43} Second, the chosen form of the penetrance function is based on an RR between carriers and noncarriers that is constant within 10-year age intervals. We have also explored more parsimonious parameterization, which gave similar results. We present the nonparametric results to avoid artifacts that may be introduced by specific parameterization.

A limitation of our study is the lack of further ethnicity indicators beyond Ashkenazim. Minority groups, such as the African Americans, are often under-represented in breast cancer studies.^{44,45} Families of African ancestry have recently been shown to have a different mutation spectrum than that of well-studied populations.⁴⁶ However, the performance of the carrier probability prediction software BRCAPRO is similar among families of different ethnic origins, suggesting similarity in genetic characteristics despite the difference in mutation spectra.

In summary, we found that the penetrance of *BRCAMutations* in the United States is largely consistent with previous studies on Western populations given the large CIs on existing estimates. However, the absolute cumulative risks are on the lower end of the spectrum.^{13–19,35} Women newly diagnosed with breast or ovarian cancer can directly use our results to understand the implications for their risk of carrying a *BRCA1/2* mutation. Asymptomatic women in whom mutations have been identified can use our results to understand their risk of developing breast and ovarian cancer, both before and after prophylactic oophorectomy.

Acknowledgements

Supported in part by the National Cancer Institute Cancer Genetics Network. Also supported in part by National Cancer Institute grant Nos. P50CA88843, P50CA62924-05, 5P30 CA06973-39, and R01CA105090 and National Institutes of Health grant No. HL 99-024 and the Hecht Fund (G.P., S.C., T.F.). Work of investigators from Georgetown University was partly supported by Cancer Genetics Network grant No. CA78146-01 and by the Familial Cancer Registry Shared Resource of the Lombardi Comprehensive Cancer Center, which receives partial support from National Institutes of Health grant No. P30-CA-51008. D.F. is supported by Cancer Genetics Network grant No. CA78284.

References

1. Martin A, Blackwood M, Antin-Ozerkis D, et al. Germline mutations in BRCA1 and BRCA2 in breast-ovarian families from a breast cancer risk evaluation clinic. *J Clin Oncol* 2001;19:2247–2253. [PubMed: 11304778]
2. Szabo CI, King MC. Population genetics of BRCA1 and BRCA2. *Am J Hum Genet* 1997;60:1013–1020. [PubMed: 9150148]
3. Newman B, Millikan RC, King MC. Genetic epidemiology of breast and ovarian cancers. *Epidemiol Rev* 1997;19:69–79. [PubMed: 9360904]
4. Claus EB, Schildkraut JM, Thompson WD, et al. The genetic attributable risk of breast and ovarian cancer. *Cancer* 1996;77:2318–2324. [PubMed: 8635102]
5. Couch FJ, DeShano ML, Blackwood MA, et al. BRCA1 mutations in women attending clinics that evaluate the risk of breast cancer. *N Engl J Med* 1997;336:1409–1415. [PubMed: 9145677]
6. Spitzer E, Abbaszadegan M, Schmidt F, et al. Detection of BRCA1 and BRCA2 mutations in breast cancer families by a comprehensive two-stage screening procedure. *Int J Cancer* 2000;85:474–481. [PubMed: 10699917]
7. Chang-Claude J, Becher H, Caligo M, et al. Risk estimation as a decision-making tool for genetic analysis of the breast cancer susceptibility genes: EC demonstration project on familial breast cancer. *Dis Markers* 1999;15:53–65. [PubMed: 10595253]
8. Karp S. Clinical management of BRCA1-and BRCA2-associated breast cancer. *Semin Surg Oncol* 2000;18:296–304. [PubMed: 10805951]
9. Burke W, Daly M, Garber J, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer: II. BRCA1 and BRCA2—Cancer Genetics Studies Consortium. *JAMA* 1997;277:997–1003. [PubMed: 9091675]
10. Easton DF, Ford D, Bishop DT. Breast and ovarian cancer incidence in BRCA1-mutation carriers. *Am J Hum Genet* 1995;56:265–271. [PubMed: 7825587]
11. Easton DF, Bishop DT, Ford D, et al. Genetic linkage analysis in familial breast and ovarian cancer: Results from 214 families. *Am J Hum Genet* 1993;52:678–701. [PubMed: 8460634]
12. Narod S, Ford D, Devilee P, et al. An evaluation of genetic heterogeneity in 145 breast-ovarian cancer families: Breast Cancer Linkage Consortium. *Am J Hum Genet* 1995;56:254–264. [PubMed: 7825586]
13. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the BRCA1 and BRCA2 genes in breast cancer families. *Am J Hum Genet* 1998;62:676–689. [PubMed: 9497246]
14. Struwing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi -Jews. *N Engl J Med* 1997;336:1401–1408. [PubMed: 9145676]
15. Hopper J, Southey M, Dite G, et al. Population-based estimate of the average age-specific cumulative risk of breast cancer for a defined set of protein-truncating mutations in BRCA1 and BRCA2: Australian Breast Cancer Family Study. *Cancer Epidemiol Biomarkers Prev* 1999;8:741–747. [PubMed: 10498392]
16. Satagopan J, Offit K, Foulkes W, et al. The lifetime risks of breast cancer in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. *Cancer Epidemiol Biomarkers Prev* 2001;10:467–473. [PubMed: 11352856]
17. Antoniou A, Pharoah PDP, Narod S, et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: A combined analysis of 22 studies. *Am J Hum Genet* 2003;72:1117–1130. [PubMed: 12677558]

18. King MC, Marks JH, Mandell JB. Breast and ovarian cancer risks due to inherited mutations in BRCA1 and BRCA2. *Science* 2003;302:643–646. [PubMed: 14576434]
19. Satagopan J, Boyd J, Kauff N, et al. Ovarian cancer risk in Ashkenazi Jewish carriers of BRCA1 and BRCA2 mutations. *Clin Cancer Res* 2002;8:3776–3781. [PubMed: 12473589]
20. Anglian Breast Cancer Study Group. Prevalence and penetrance of BRCA1 and BRCA2 mutations in a population-based series of breast cancer cases. *Br J Cancer* 2000;83:1301–1308. [PubMed: 11044354]
21. Kraft P, Thomas DC. Bias and efficiency in family-based gene-characterization studies: Conditional, prospective, retrospective, and joint likelihoods. *Am J Hum Genet* 2000;66:1119–1131. [PubMed: 10712222]
22. Parmigiani G, Berry DA, Aguilar O. Determining carrier probabilities for breast cancer susceptibility genes BRCA1 and BRCA2. *Am J Hum Genet* 1998;62:145–158. [PubMed: 9443863]
23. Fay MP, Pfeiffer R, Cronin KA, et al. Age-conditional probabilities of developing cancer. *Stat Med* 2003;22:1837–1848. [PubMed: 12754719]
24. National Cancer Institute. Surveillance, Epidemiology, and End Results (SEER) Program. <http://www-seer.ims.nih.gov>
25. Whittemore A, Halpern J. Logistic regression of family data from retrospective study designs. *Genet Epidemiol* 2003;25:177–189. [PubMed: 14557986]
26. Iversen ES, Chen S. Population-calibrated gene characterization: Estimating age at onset distributions associated with cancer genes. *J Am Stat Assoc* 2005;100:399–409. [PubMed: 18418465]
27. Roa BB, Boyd AA, Volcik K, et al. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. *Nat Genet* 1996;14:185–187. [PubMed: 8841191]
28. Oddoux C, Struwing JP, Clayton CM, et al. The carrier frequency of the BRCA2 6174delT mutation among Ashkenazi Jewish individuals is approximately 1%. *Nat Genet* 1996;14:188–190. [PubMed: 8841192]
29. Fodor FH, Weston A, Bleiweiss IJ, et al. Frequency and carrier risk associated with common BRCA1 and BRCA2 mutations in Ashkenazi Jewish breast cancer patients. *Am J Hum Genet* 1998;63:45–51. [PubMed: 9634504]
30. Andersen TI. Genetic heterogeneity in breast cancer susceptibility. *Acta Oncol* 1996;35:407–410. [PubMed: 8695152]
31. Antoniou AC, Pharoah PDP, McMullan G, et al. A comprehensive model for familial breast cancer incorporating BRCA1, BRCA2 and other genes. *Br J Cancer* 2002;86:76–83. [PubMed: 11857015]
32. Chen S, Wang W, Broman K, et al. Bayes-Mendel: An R environment for Mendelian risk prediction. *Stat Appl Genet Mol Biol* 2004;3:1–19.
33. Parmigiani, G. *Modeling in Medical Decision Making*. Chichester: United Kingdom, Wiley; 2002.
34. Murphy EA, Mutalik GS. The application of Bayesian methods in genetic counseling. *Hum Hered* 1969;19:126–151.
35. Marroni F, Aretini P, D'Andrea E, et al. Penetrances of breast and ovarian cancer in a large series of families tested for BRCA1/2 mutations. *Eur J Hum Genet* 2004;12:899–906. [PubMed: 15340362]
36. Antoniou AC, Pharoah PPD, Smith P, et al. The BOADICEA model of genetic susceptibility to breast and ovarian cancer. *Br J Cancer* 2004;91:1580–1590. [PubMed: 15381934]
37. Rebbeck TR, Lynch HT, Neuhausen SL, et al. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N Engl J Med* 2002;346:1616–1622. [PubMed: 12023993]
38. Tomlinson GE, Schorge J, Robinson L, et al. Risk reduction practices after BRCA1/2 testing. *Proc Am Soc Clin Oncol* 2003;22:97.(suppl: abstr 387)
39. Schwartz MD, Kaufman E, Peshkin BN, et al. Bilateral prophylactic oophorectomy and ovarian cancer screening following BRCA1/BRCA2 mutation testing. *J Clin Oncol* 2003;21:4034–4041. [PubMed: 14581427]
40. Kramer J, Velazquez I, Chen B, et al. Prophylactic oophorectomy reduces breast cancer penetrance during prospective, long-term follow-up of brca1 mutation carriers. *J Clin Oncol* 2005;23:8629–8635. [PubMed: 16314625]
41. Scheuer L, Kauff N, Robson M, et al. Outcome of preventive surgery and screening for breast and ovarian cancer in BRCA mutation carriers. *J Clin Oncol* 2002;20:1260–1268. [PubMed: 11870168]

42. Claus E, Schildkraut J, Iversen EJ, et al. The effect of BRCA1 and BRCA2 on the association between breast cancer risk and family history. *J Natl Cancer Inst* 1998;90:1824–1829. [PubMed: 9839523]
43. Antoniou AC, Gayther SA, Stratton JF, et al. Risk models for familial ovarian and breast cancer. *Genet Epidemiol* 2000;18:173–190. [PubMed: 10642429]
44. Hughes C, Peterson SK, Ramirez A, et al. Minority recruitment in hereditary breast cancer research. *Cancer Epidemiol Biomarkers Prev* 2004;13:1146–1155. [PubMed: 15247125]
45. Olopade OI, Fackenthal JD, Dunston G, et al. Breast cancer genetics in African Americans. *Cancer* 2003;97:236–245. [PubMed: 12491487](suppl 1)
46. Nanda R, Schumm LP, Cummings S, et al. Genetic testing in an ethnically diverse cohort of high-risk women: A comparative analysis of BRCA1 and BRCA2 mutations in American families of European and African ancestry. *JAMA* 2005;294:1925–1933. [PubMed: 16234499]

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF (via Adobe® Acrobat Reader®) version.

Fig 1.

Future risks of developing cancer for a female carrier at a range of ages in the next 10-year interval, 20-year interval, and so on. (A) Breast cancer, *BRCA1* carrier; (B) breast cancer, *BRCA2* carrier; (C) ovarian cancer, *BRCA1* carrier; and (D) ovarian cancer, *BRCA2* carrier. For example, in the upper left panel, the left-most curve gives the risk of developing breast cancer for a 20-year-old *BRCA1* mutation carrier in the next 10 to 50 years. The vertical bars are 95% CIs.

Fig 2.

Mean relative risks for US carriers to noncarriers with 95% CIs. The noncarrier incidences are from the Surveillance, Epidemiology and End Results age-conditional probabilities of developing cancer. (A) Breast cancer, *BRCA1* carrier; (B) breast cancer, *BRCA2* carrier; (C) ovarian cancer, *BRCA1* carrier; and (D) ovarian cancer, *BRCA2* carrier.

Table 1

Families in the CGN Study by Source

Center	No. of Families		
	Non-AJ	AJ	Total
Georgetown University	160	90	250
University of Pennsylvania	556	179	735
Duke University	238	25	263
Johns Hopkins University	57	47	104
Baylor College of Medicine	0	282	282
M.D. Anderson Cancer Center	73	29	102
University of Texas Southwestern Medical School	86	22	108
Huntsman Cancer Institute	102	2	104
Total	1,272	676	1,948

Abbreviations: CGN, Cancer Genetics Network; AJ, Ashkenazi Jew.

Table 2

Overall Characteristics of Counselees

Characteristic	% of Counselees
Age, years	
Mean	52.8
Standard deviation	13.1
Male	2.7
Diagnosed with breast cancer	65.5
Diagnosed with ovarian cancer	8.7
Unaffected	28.2
<i>BRCA1</i> mutation carriers, estimated*	14.6
<i>BRCA2</i> mutation carriers, estimated*	7.4

* Estimates account for underreporting of mutation as a result of imperfect sensitivity of the genotyping methods used.

Table 3**BRCA1**and *BRCA2* Genotyping Methods and Associated Sensitivities Used in the Calculations

Genotyping Method	No. of Families Tested	Sensitivity
<i>BRCA1</i>		
SSCP	209	0.46
Sequencing	466	0.82
Targeted mutation screening	8	0.80
Sequencing for mutations 185delAG and 5382insC	10	0.82
CSGE	378	0.60
SSCP + ASO	18	0.67
Targeted mutation screening + sequencing	60	0.90
Targeted mutation screening + CSGE	21	0.89
Other	28	0.93
<i>BRCA2</i>		
SSCP	178	0.47
Sequencing	509	0.77
CSGE	260	0.50
ASO	9	0.68
ASO + CSGE	18	0.73
ASO + sequencing	60	0.88
Other	63	0.87

Abbreviations: SSCP, single-strand conformation polymorphism analysis; CSGE, conformation sensitive gel electrophoresis; ASO, allele-specific oligohybridization.

Table 4
Penetrance: Age-Specific Cumulative Risks of Developing Cancer for Mutation Carriers and Noncarriers

Age (years)	Breast Cancer Risk					Ovarian Cancer Risk				
	BRCA1		BRCA2			BRCA1		BRCA2		
	%	95% CI	%	95% CI	None (%)	%	95% CI	%	95% CI	None (%)
30	3.4	1.8 to 5	1.5	0.66 to 2.7	0.011	NE	3.1 to 6.7	NE	0.72 to 3.8	0.026
40	14	11 to 18	11	8.2 to 15	0.12	4.7	9.7 to 17	1.9	2.2 to 6.2	0.068
50	28	24 to 34	23	19 to 29	0.72	13	22 to 35	4	6.5 to 17	0.16
60	41	35 to 48	39	32 to 46	2.4	28	30 to 50	11	14 to 32	0.36
70	46	39 to 54	43	36 to 51	5.0	39		22		0.68

NOTE. The noncarrier risks are calculated from the Surveillance, Epidemiology, and End Results incidence for the US population.
Abbreviation: NE, not estimated.

Table 5

Predicted Cancer Risk for a Female Mutation Carrier

Current Age (years)		Risk of Developing Cancer to Age <i>t</i>											
		<i>t</i> = 29 Years			<i>t</i> = 39 Years			<i>t</i> = 49 Years			<i>t</i> = 59 Years		
		%	95% CI		%	95% CI		%	95% CI		%	95% CI	
<i>BRCA1</i> breast													
20	2.5	1.3 to 3.7		12	9.3 to 15		26	22 to 31		38	32 to 45		43
30				10	7.6 to 13		24	20 to 29		37	31 to 43		42
40							16	12 to 20		30	24 to 37		36
50										17	13 to 23		24
60													9.1
<i>BRCA2</i> breast													
20	1.1	0.46 to 2		9.2	6.8 to 13		21	17 to 26		36	30 to 43		41
30				8.3	6 to 12		20	16 to 25		36	29 to 42		40
40							13	10 to 17		30	24 to 37		35
50										20	14 to 26		26
60													7.9
<i>BRCA1</i> ovarian													
20	1.2	1.2 to 1.2		3.6	2.2 to 5.3		11	8.1 to 15		25	19 to 31		35
30				2.5	1.1 to 4.2		10	7 to 14		24	18 to 30		34
40							7.8	5.2 to 11		22	16 to 29		33
50										16	11 to 22		28
60													15
<i>BRCA2</i> ovarian													
20	0.15	0.15 to 0.15		1.6	0.56 to 3.2		3.5	1.9 to 5.6		9.5	5.8 to 15		19
30				1.5	0.41 to 3.1		3.4	1.7 to 5.5		9.4	5.7 to 14		18
40							2	0.98 to 3.4		8.2	4.5 to 13		17
50										6.5	3 to 12		16
60													11

Table 6

Relative Risk of Cancer

Age (years)	Breast Cancer				Ovarian Cancer			
	BRCA1		BRCA2		BRCA1		BRCA2	
	Relative Risk	95% CI	Relative Risk	95% CI	Relative Risk	95% CI	Relative Risk	95% CI
20-29	106	56 to 161	46	19 to 85	NE	16 to 76	NE	7 to 57
30-39	44	33 to 58	38	27 to 54	43	27 to 54	27	27
40-49	15	11 to 20	13	9 to 17	65	42 to 95	15	6.4 to 27
50-59	8.2	5.5 to 12	9.8	6.3 to 14	68	45 to 96	27	12 to 52
60-69	2.8	0.48 to 5.5	2.1	0.16 to 4.5	45	21 to 78	34	14 to 68

Bayes Factor for Counseling An Individual Immediately After Diagnosis in Absence of Other Information About Her Family*

Table 7

Age (years)	Breast Cancer				Ovarian Cancer			
	BRCA1		BRCA2		BRCA1		BRCA2	
	Bayes Factor	95% CI	Bayes Factor	95% CI	Bayes Factor	95% CI	Bayes Factor	95% CI
25	106	56 to 159	46	19 to 84	NE	NE	NE	NE
35	42	31 to 54	36	26 to 51	42	16 to 73	26	7.1 to 56
45	13	9.5 to 16	11	7.9 to 14	60	40 to 87	15	6.3 to 26
55	5.6	3.9 to 7.8	7.1	4.7 to 9.7	55	38 to 76	26	11 to 48
65	1.7	0.29 to 3.1	1.3	0.1 to 2.8	30	15 to 50	29	12 to 56

Abbreviation: NE, not estimated.

* This is the probability of her developing cancer by age t , conditioning on carrying a mutation, divided by the same probability conditioning on her not carrying a mutation.

Table 8
Predicted Cancer Risk for a Female Mutation Carrier Who Has Undergone Bilateral Prophylactic Oophorectomy

Current Age (years)	Risk of Developing Cancer to Age <i>t</i>											
	<i>t</i> = 29 Years			<i>t</i> = 39 Years			<i>t</i> = 49 Years			<i>t</i> = 59 Years		
	%	95% CI		%	95% CI		%	95% CI		%	95% CI	
<i>BRCA1</i> breast												
20	1.2	0.62 to 1.8		5.9	4.5 to 7.4		13	11 to 16		20	17 to 24	
30				4.8	3.6 to 6.2		12	9.9 to 15		19	16 to 23	
40							7.8	6 to 9.9		16	12 to 19	
50										8.6	6.1 to 12	
60												4.4
												1.6 to 7.5
<i>BRCA2</i> breast												
20	0.51	0.22 to 0.94		4.4	3.2 to 6.1		11	8.3 to 13		19	15 to 23	
30				4	2.9 to 5.6		10	8 to 13		19	15 to 23	
40							6.5	4.9 to 8.5		15	12 to 19	
50										9.7	6.7 to 13	
60												3.8
												1.4 to 6.6
<i>BRCA1</i> ovarian												
20	0.048*			0.15	0.09 to 0.22		0.47	0.34 to 0.62		1.1	0.84 to 1.5	
30				0.1	0.043 to 0.17		0.42	0.29 to 0.58		1.1	0.8 to 1.4	
40							0.32	0.21 to 0.47		0.99	0.71 to 1.3	
50										0.68	0.46 to 0.96	
60												1.3
												0.85 to 1.9
												0.34 to 1.1
<i>BRCA2</i> ovarian												
20	0.0062*			0.064	0.022 to 0.13		0.14	0.075 to 0.23		0.4	0.24 to 0.62	
30				0.058	0.016 to 0.12		0.14	0.069 to 0.23		0.4	0.23 to 0.62	
40							0.08	0.039 to 0.14		0.34	0.18 to 0.57	
50										0.27	0.12 to 0.5	
60												0.71
												0.39 to 1.1
												0.2 to 0.88

* Width of the CI is ignorable.