Adjusting the estimated proportion of breast cancer cases associated with *BRCA1* and *BRCA2* mutations: Public health implications

Monica R. McClain, PhD[1], Glenn E. Palomaki, BS[1], Katherine L. Nathanson, MD[2], and James E. Haddow, MD[1]

Purpose: Mutations in *BRCA1* or *BRCA2* genes increase breast cancer risk. Assuring reliability of information about these mutations is increasingly important to the health care community; mutation testing is becoming more widespread. We describe a methodology for assessing such information. **Methods:** Our approach integrates four interdependent epidemiologic parameters: (1) the probability of developing breast cancer, (2) the proportion of breast cancer cases with a *BRCA1* or *BRCA2* mutation, (3) the proportion of women that carries a mutation, and (4) the proportion of women with a mutation that develops cancer. We assess the plausibility of estimates of these parameters from published reports and commonly accessed information sources. **Results:** Assuming a fixed probability of developing breast cancer, the following estimates for the other three epidemiologic parameters are derived for women by age 70: 1% to 2% of all breast cancer cases are associated with a *BRCA1* or *BRCA2* mutation; 1 in 300 to 1 in 465 women carry a mutation; and 35 to 65% of mutation carriers develop breast cancer. Within these ranges, however, only selected combinations are plausible. The proportion of mutation-related breast cancer is lower than listed in some common information sources (1 to 2% vs 6%). Also, penetrance is somewhat lower and the carrier rate somewhat higher. **Conclusions:** The four epidemiologic parameters can be integrated to test their plausibility. *BRCA1* and *BRCA2* mutations are associated with only one-third as many breast cancer cases in the general population as reported by commonly accessed information sources. *Genet Med* 2005:7(1):28–33.

Key Words: *breast cancer, genetics, public health,* BRCA *mutations.*

Guidelines have been developed to aid clinicians in deciding when to offer *BRCA1* and *BRCA2* mutation testing.[1–6] These guidelines recommend testing in specific circumstances, such as in women whose family history indicates an inherited predisposition to breast cancer. When a mutation is identified in an index case, cascade testing can be offered to other family members, thereby allowing primary prevention options to be considered. Implementation of *BRCA1* and *BRCA2* mutation testing by primary care providers has been sporadic and driven, in part, by direct-to-consumer advertising.[7–11]

At least two information sources about *BRCA1* and *BRCA2* mutation testing have been developed for use by primary care providers in the United States.[12,13] In addition, two comprehensive reviews on *BRCA1* and *BRCA2* and hereditary breast cancer are available via internet access to health care providers, as well as the general public.[14,15] The data summarized by these sources are not always complete and/or consistent, either in-

ternally or with each other. These data are composed of three epidemiologic parameters: (1) the penetrance of *BRCA1* and *BRCA2* mutations, (2) the mutation carrier rate in the general population, and (3) the proportion of all breast cancer cases that is associated with a mutation. Almost all estimates quoted for each of these epidemiologic parameters are indirectly derived in the original studies. For example, there have been no published studies where a large population-based sample has been selected and undergone mutation testing to determine the prevalence of mutation carriers (with the exception of individuals of Ashkenazi Jewish heritage[16–21]). Thus, this mutation carrier rate has been estimated indirectly. Similarly, an unbiased way to determine penetrance is a prospective study of individuals with and without mutations who are followed to see who does and does not develop breast cancer. Current penetrance estimates may be biased because they have been inferred by comparing family history in *BRCA* mutation carriers to that in individuals without mutations, using women with breast cancer as the index case.

The present analysis is based on recognition that estimates for these three epidemiologic parameters, along with a fourth—the probability of developing breast cancer in the general population—are interdependent and that these relationships can be used to evaluate and refine the estimates. By integrating all four parameters, an initial evaluation indicates that

one or more of the estimates from the information sources must be incorrect. To our knowledge, this is the first attempt to reconcile published estimates of these parameters in the context of a cohesive, integrated approach.

MATERIALS AND METHODS

The four epidemiologic parameters used in our integrated approach are described below and summarized in Table 1.

(1) Probability of developing breast cancer (cumulative incidence)

We first estimated the proportions of a cohort of one million 20-year-old women in the United States general population that will develop breast cancer: (1) by age 45 and (2) by age 70. These were computed by the DevCan software,[22] using the age-conditional probabilities by 5-year intervals.[23] Twenty years of age was selected as the reference point because *BRCA1* and *BRCA2* mutation testing is recommended almost exclusively for adults and the incidence of breast cancer prior to age 20 is nearly zero. We selected 45 years as one cutoff because the studies on *BRCA1* or *BRCA2* mutations in early onset breast cancer enrolled women diagnosed between the ages of 35 and 55 years.[24–28] We selected 70 years because it is the most com-

mon age cutoff used in studies reporting the proportion of women with a mutation that develops breast cancer.

(2) Proportion of women with breast cancer that has a *BRCA1* or *BRCA2* mutation (clinical sensitivity)

Direct estimates have been made for the proportion of early-onset breast cancer with these mutations.[24–28] The adjusted range of these direct estimates is reported in Table 1. The details of how adjustments were made to these estimates are shown in the Appendix. These conservative adjustments account for deleterious mutations that have been missed because the studies used methodologies that are less sensitive than the gold standard of direct DNA sequencing. The adjustments do not account for mutations that are not detectable by sequencing. The estimates of clinical sensitivity are heterogeneous. Therefore, rather than calculating a summary estimate, we have provided a sensitivity analysis over the range of published estimates in our integrated approach. Sensitivity analysis is appropriate when there is not consensus around what value should be assigned to a given parameter.

The proportion of breast cancer cases by age 70 associated with *BRCA1* mutations is derived from both direct[29,30] and indirect[31,32] estimates, whereas only indirect estimates have been reported for the contribution of mutations in both *BRCA1* and *BRCA2* genes to breast cancer.[28,33,34] The range of these estimates is also shown in Table 1. We include a sensitivity analysis for this estimate, as well, in our integrated approach.

(3) Proportion of women with a *BRCA1* or *BRCA2* mutation that develops breast cancer (penetrance)

Estimates have been reported in both population-based individuals and high risk families.[25,35–44] Table 1 shows that these point estimates cover a broad range. The corresponding confidence intervals are also wide, indicating that the estimates are not precise. Biases are inherent in the study designs used to produce these estimates.[45] For these reasons, we also include a sensitivity analysis for this variable in our integrated approach. In our analysis, separate mutation penetrance estimates are used for the two age cutoffs. By age 45, the penetrance of *BRCA1* mutations is higher than for *BRCA2* mutations, but only 40 out of every 100 mutation carriers will have a *BRCA1* mutation, based on the estimated prevalence of mutations (see no. 4). For this age cutoff, our integrated approach utilizes a weighted average of the population-based penetrance estimates. There is no consensus among the studies on the *BRCA1* and *BRCA2* mutation penetrance estimates for breast cancer by age 70. Of the three population-based studies that provide penetrance estimates for mutations in both genes in the non-Ashkenazi Jewish population, two report higher estimates for *BRCA2* mutations[25,36] and one reports a lower estimate.[35] For our analysis, the penetrance estimates for *BRCA1* and *BRCA2* mutations are assumed to be the same for breast cancer by the age of 70.

Table 1

Ranges of published values for four epidemiologic parameters that characterize the relationship between *BRCA1* and *BRCA2* mutations and breast cancer

Epidemiologic parameter and definition	By age 45 years	By age 70 years
Cumulative incidence (%)	1.19	9.67
Proportion of women in the general population that will develop breast cancer by a given age[22]		
Clinical sensitivity (%)	5.4–12.6[24–28]	2–10[28–34]
Proportion of women with breast cancer in the general population that has a *BRCA1* or *BRCA2* mutation by a given age		
Penetrance (%)		
Proportion of women with a *BRCA1* or *BRCA2* mutation that develops breast cancer by a given age		
BRCA1 alone[25,35–39,41]	20–40	35–85
BRCA2 alone[25,35–37,41,43]	10–25	45–85
BRCA1 and BRCA2[25,35–37]	15–30[a]	35–65[a]
Carrier rate		
The rate of women with a *BRCA1* or *BRCA2* mutation in the general population		
BRCA1 alone[25,28,32,36,37]	1 in 800 to 1 in 1,400	
BRCA2 alone[25,28,36,37]	1 in 450 to 1 in 800	
BRCA1 and BRCA2[25,28,31,36,37]	1 in 300 to 1 in 450	

[a]Approximate weighted average of the penetrance for *BRCA1* and *BRCA2* from population based studies.

(4) Proportion of women with *BRCA1* and *BRCA2* mutations in the general population (carrier rate)

This proportion has been estimated indirectly by several studies[25,28,31,32,36,37] and can be expressed as a carrier rate (e.g., 0.2% = 1 in 500). Table 1 shows the range of these estimates.

The relationship among the four epidemiologic parameters is based on Bayes theorem and is defined by our integrated approach as:

$$\text{carrier rate (1 in } N) = \frac{1}{(c_i \times c_s)/p,}$$

where c_i = cumulative incidence of breast cancer (%) by a given age, c_s = clinical sensitivity of *BRCA1/2* mutations (%), and p = penetrance of *BRCA1/2* mutations (%). Any three of these epidemiologic parameter estimates can be used to compute the fourth. This integrated approach is then applied to data from original research studies and to commonly accessed information sources that provide a review of these data.

RESULTS

Table 2 shows a two-way sensitivity analysis for penetrance of *BRCA1* and *BRCA2* mutations and the proportion of breast cancer cases with a mutation. The top half of the table uses the cumulative incidence of cancer in the general U.S. population by age 45 years (1.19%), whereas the bottom half uses the cumulative incidence by age 70 years (9.67%). The upper and lower limits for proportions of breast cancer cases with a mutation (columns) and penetrance (rows) are taken from Table 1. The associated carrier rates (table entries) are then computed for each combination. For example, by age 45 years, with mutations present in 5% of cancer cases and a penetrance of 25%, the carrier rate is computed to be 1 in 420 women (boxed

entry in top half of Table 1). Fig. 1 shows how these calculations are made. As the proportion of cancers associated with a mutation increases, the carrier rate must also increase. However, as the penetrance increases, the carrier rate must decrease.

In order to focus on plausible combinations of three of the epidemiologic parameters, we have bolded selected entries in Table 2 when the four parameters are internally consistent (e.g., the computed carrier rate based on the other parameters is within the range of published carrier rates specified in Table 1). Columns showing the proportion of breast cancer cases associated with mutations of 9% or higher are not shown, because none of the corresponding carrier rates are within the range specified. According to this analysis, between 4% and 8% of breast cancer cases by age 45 occur in women with a *BRCA1* or *BRCA2* mutation.

In the bottom half of Table 2, the range of carrier rates validated for the 45 year age group is used to help select reasonable and consistent combinations of penetrance and proportions of cancers by age 70 that are associated with mutations. The range of penetrance estimates is again taken from Table 1. Entries are bolded, if they are internally consistent. When the proportion of breast cancer cases associated with mutations exceeds 2%, none of the corresponding carrier rates are within the range specified in Table 1. According to this integrated approach, the proportion of women with breast cancer by age 70 that has a *BRCA1* or *BRCA2* mutation is between 1 and 2%.
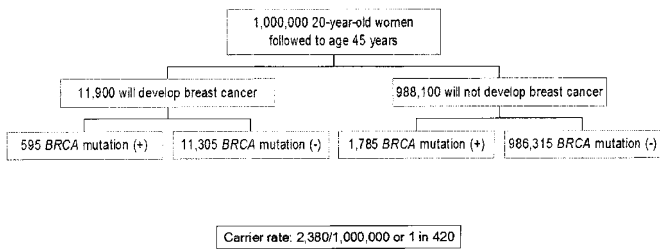
The top half of Table 3 compares the epidemiologic parameter estimates reported by the four information sources commonly used by health care providers and patients. Only one of these sources cites estimates for all four of the epidemiologic parameters.[12] The bottom half of Table 3 shows estimates derived using our integrated approach for all four epidemiologic

Table 2
BRCA1 and *BRCA2* mutation carrier rates computed using the interrelationships among the cumulative incidence of breast cancer, the proportion of women with breast cancer that has a mutation, and the penetrance of mutations

Breast cancer by age 45 years (cumulative incidence = 1.19%)

| Penetrance (%) | Proportion of Women with Breast Cancer that has a *BRCA1* or *BRCA2* Mutation | | | | |
	4%	5%	6%	7%	8%
15	**1 in 315**	1 in 250	1 in 210	1 in 180	1 in 160
20	**1 in 420**	**1 in 340**	1 in 280	1 in 240	1 in 210
25	1 in 525	1 in 420	**1 in 350**	**1 in 300**	1 in 260
30	1 in 630	1 in 505	**1 in 420**	**1 in 360**	**1 in 315**

Breast cancer by age 70 years (cumulative incidence = 9.67%)

| Penetrance (%) | Proportion of Women with Breast Cancer that has a *BRCA1* or *BRCA2* Mutation | | | | |
	1.00%	1.25%	1.50%	1.75%	2.00%
35	**1 in 360**	1 in 290	1 in 240	1 in 205	1 in 180
45	**1 in 465**	**1 in 370**	**1 in 310**	1 in 265	1 in 235
55	1 in 570	**1 in 455**	**1 in 380**	**1 in 325**	1 in 285
65	1 in 670	1 in 540	**1 in 450**	**1 in 395**	**1 in 335**

Bolded items represent plausible combinations of the four epidemiologic parameter estimates and boxed item represents the combination used in Fig. 1 (see text).

1,000,000 20-year-old women
followed to age 45 years

11,900 will develop breast cancer | 988,100 will not develop breast cancer

595 *BRCA* mutation (+) | 11,305 *BRCA* mutation (−) | 1,785 *BRCA* mutation (+) | 986,315 *BRCA* mutation (−)

Carrier rate: 2,380/1,000,000 or 1 in 420

Fig. 1. Flowchart showing an example of how the cumulative incidence of breast cancer and the three epidemiologic parameters are related. In this example, a hypothetical cohort of one million women is followed from age 20 to age 45. Overall, 11,900 cases of breast cancer are expected (cumulative incidence). Among these 11,900 women with breast cancer, 595 (5%) will have a *BRCA1* or *BRCA2* mutation (clinical sensitivity). When the penetrance estimate of 25% is applied, 2,380 women carry a mutation (595 / 0.25). Thus, 1,785 women with a mutation have not developed breast cancer by age 45 (2,380 − 595). The carrier rate is, therefore, 1 in 420. Numbers in the remaining boxes in Fig. 1 are computed by subtraction.

parameters when the other three parameters are set to the values in the top half of Table 3. The carrier rate is computed to be between 1 in 133 and 1 in 207 when the cumulative incidence of breast cancer is 7%, the proportion of cancer cases with a mutation is 6% and penetrance is allowed to vary from 56 to 87%. The proportion of cancer cases with a mutation is computed to be between 1.6 and 2.5% when the cumulative incidence of breast cancer is 7%, the carrier rate is 1 in 500 and the penetrance is allowed to vary between 56% and 87%. The penetrance is computed to exceed 100% (not plausible) when the cumulative incidence of breast cancer is 7%, the proportion of cancer cases with a mutation is 6% and the carrier rate is 1 in 500.

These computations demonstrate that epidemiologic estimates from one of the four information sources are not internally consistent.[12] Neither the computed carrier rate nor the computed penetrance are plausible, indicating that the proportion of cancer cases with a mutation in the top half of the table must be overestimated. Although the reported value of 6% is in the middle of the published range of 2% to 10% (Table 1), our analysis shows that the most plausible value is between 1% and 2%.

DISCUSSION

We developed the integrated approach described above to reconcile individual estimates that each have varying degrees of reliability. Our study confirms published estimates showing a combined carrier rate for *BRCA1* and *BRCA2* mutations in the general population of approximately 1 in 400. For women up to age 45, the mutation penetrance also falls within the range reported by published population-based studies, but as expected, it is lower than the reported estimates in high-risk families. Also, the proportion of women with breast cancer by age 45 that carries a mutation is between 4% and 8%, near the lower end of the published range. For women with breast cancer by age 70, the proportion with a *BRCA1* or *BRCA2* mutation is between 1% and 2%. This estimate is similar to the two studies that directly measured clinical sensitivity of *BRCA1*

mutations,[29,30] but is lower than would be expected had *BRCA2* mutations been identified, as well. The estimate of 1% to 2% is just below the lower end of the range in the published literature that indirectly estimated clinical sensitivity and considerably below the estimates provided by some of the most commonly available information sources. The studies that indirectly estimated the clinical sensitivity were all published within 5 years of the cloning of *BRCA1*.[28,31–34] The estimates derived from these studies may be higher due to the indirect methods used and/or the limited data available on *BRCA1* and *BRCA2* mutations at that time. The clinical sensitivity estimate that is reported by some of the common information sources[12,13] references an early study that estimated the contribution of *BRCA1* and *BRCA2* mutations to breast cancer in families with at least four cases of breast cancer.[41] This estimate is higher than those derived from cancer cases in the general population.

Studies that are composed mainly of Ashkenazi Jewish women are not included in our analysis, because at least one epidemiologic parameter (mutation carrier rate) is higher by about a factor of 10. Also, the cumulative incidence of breast cancer is less well defined in this group. These factors indicate that this group of women should be considered separately. The studies that provided estimates for the epidemiologic parameters used in our integrated approach included primarily Caucasian women in the United States or Western Europe. Therefore, analyses involving other ethnic/racial groups may yield different results.

Our approach can be applied, however, to other groups (e.g., Ashkenazi Jewish women), taking into account special considerations such as the important impact of founder mutations on the carrier rate and, perhaps, genotype/phenotype relationships. Another application might involve *BRCA1* and *BRCA2* mutation testing in the presence of a family history of breast and/or ovarian cancer combined. An extended approach could be created that addresses such mutation testing for breast and/or ovarian cancer. This approach might also be adapted to other disorders with a genetic component.

There are several limitations to our integrated approach. First, the penetrance estimates for *BRCA1* and *BRCA2* mutations are combined. There are substantial differences in penetrance for early onset breast cancer between mutations in each gene that we address by utilizing a weighted average. It is not yet clear if there are differences in penetrance for breast cancer by age 70. We assume that the penetrance is the same for mutations in *BRCA1* and *BRCA2*. However, even if the penetrance estimate is 65% higher for mutations in one gene compared with the other, the impact on clinical sensitivity is < 1%. Another approach could be to consider mutations in each gene separately. Furthermore, there may be variations in penetrance by mutation type (e.g., frameshift, nonsense) or mutation position (e.g., ovarian cancer cluster region).[41,46–49] Second, the use of Surveillance, Epidemiology, and End Results data in the DevCan software is the only estimate of breast cancer incidence in the U.S. that is generalizeable to the general population. The majority of studies that estimate mutation pen-

Table 3
Breast cancer and *BRCA1/BRCA2* mutations for women up to age 70 years: A comparison among commonly used information sources

Epidemiologic parameter	Myriad[12]	American Medical Association[13]	Physician data query[14]	Gene reviews[15]
Cumulative incidence (%)	7	Not given	Not given	Not given
Cancer cases with a mutation (%)	6	6	2	Not given
Penetrance of mutations (%)	56–87	56–87	36–85	36–86
Carrier rate (1 in *n*)	500	Not given	500	500–1000
Calculated from above[a]				
Cancer cases with a mutation (%)	1.6–2.5	Insufficient	Insufficient	Insufficient
Penetrance of mutations (%)	>100	Information	Information	Information
Carrier rate (1 in *n*)	133–207			
Internally consistent	No	Unknown	Unknown	Unknown

[a]Each epidemiologic parameter is calculated by setting the other three parameters listed by the same information source as constants in our integrated approach.

etrance have used age-specific breast cancer incidence in England and Wales.[35–37,41] Because the incidence of breast cancer is lower in these countries, the resulting penetrance estimates may not be directly applicable to the U.S. population.

This study highlights the need for accurate and complete information regarding the burden of *BRCA1* and *BRCA2* mutations on breast cancer in the U.S. Only one of the four commonly accessed information sources examined in this study contains estimates for the four epidemiologic parameters.[12] The remaining three information sources report estimates for two[13,15] or three[14] of the epidemiologic parameters. The quality of the evidence cited in support for these estimates is questionable and, in some cases, references are absent. For example, the mutation carrier rate is not cited in one information source.[13] It is cited to be between 1 in 500 and 1 in 1000 with no references by another source.[15] The third information source cites the mutation carrier rate to be 1 in 800 for *BRCA1* mutations (no reference) and 1 in 500 for all mutations but the reference given does not provide a mutation carrier rate estimate.[14] The fourth information source cites a 1 in 500 mutation carrier rate. However, the given reference is not the original data source and only quotes this carrier rate for *BRCA1* mutations.[12] None of the four information sources cite the research articles from which the mutation carrier rate is inferred, which we have summarized in this study.

Our study finds that *BRCA1* and *BRCA2* mutations appear to account for only one-third as many breast cancer cases by age 70 as reported in the two information sources for physicians. From the viewpoint of public health planning, the downward revision in this estimate means that the potential reduction in breast cancer cases resulting from mutation testing in the general population is likely to be substantially lower than generally thought.

APPENDIX

Direct sequencing is expected to have the highest clinical sensitivity of all mutation detection methods. One study used direct sequencing of *BRCA1* as the gold standard and evaluated the performance of SSCP, CSGE, two-dimensional gene scanning (TDGS), and denaturing high performance liquid chromatography (dHPLC). These four methods detected 65%, 60%, 91%, and 100% of the mutations detected by sequencing, respectively.[50] A second study that again used direct sequencing as the gold standard found that mutation analysis by SSCP accounted for 94% of the detected variants, whereas dHPLC resolved 100% of the alterations.[51] We used conservative estimates of mutation detection to adjust the clinical sensitivities of mutation testing in women with early onset breast cancer (Table 4).

Table 4
Adjustments for potential methodological underascertainment made to clinical sensitivity estimates of *BRCA1/2* mutation testing

Reference	*BRCA1/2* methodology	Estimated proportion of mutations detected (%)
Malone et al.[27]	SSCP	65
Loman et al.[26]	PTT/SSCP/dHPLC/direct sequence	80
Hopper et al.[24]	PTT/HA	85
Peto et al.[28]	CSGE	60
Anglian Breast Cancer Study Group[25]	MHA	60

Methodology: PTT/HA, Protein truncation test/Heteroduplex analysis; CSGE, Conformation-sensitive gel electrophoresis; SSCP, Single strand conformation polymorphism; MHA, Multiplex heteroduplex analysis.

their support of the ACCE project. We also thank Ingrid Hall, PhD, Division of Cancer Prevention and Control, National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention for helping support the project.

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