Re: On the Use of Familial Aggregation in Population-Based Case Probands for Calculating Penetrance

In a recent issue of the Journal (1), Begg describes potential biases in our (2) and other population-based case-screening studies that estimate mutation penetrance through kin–cohort methods (3). The main issue raised by Begg is that a case series represents individuals selected to have risk factors that place them at excess disease risk. To the extent that any risk factors are overrepresented among case relatives—because of either genetic or familial reasons—family members of both carrier and non-carrier probands will show excess disease incidence, and thus mutation penetrance will be overestimated. We agree with this theoretical argument but question the degree of bias actually present in the published studies of breast and ovarian cancer and mutations in BRCA1 or BRCA2 to which Begg refers (1). In particular, our penetrance estimates of breast cancer based on an ovarian cancer case series are unlikely to be biased (2).

Disease risk to a given age among carrier and noncarrier relatives is found by treating the relatives as a cohort and performing a Cox regression analysis on it, with age at diagnosis, death, or end of follow-up as the time variable and with proband mutation status as the exposure. This method yields an estimate of the relative risk (RR) of disease among relatives associated with proband mutation status, as well as a product-limit estimate of the survivor function for the noncarrier relatives ($S_0$). The estimated mutation penetrance is $1 + S_0 - 2(S_0)^{RR}$. This method is robust in the usual circumstances of one (or sometimes two) affected first-degree relatives per family, but generalized estimating equation methods can also be used. As Begg notes (1), the estimated RR is not subject to the bias; only $S_0$ is subject to bias. In fact, $1 + S_0 - 2(S_0)^{RR}$ estimates the penetrance for any similar base population to which the RR would apply. Therefore, for studies such as ours (2) that use this method, and in the very usual circumstances where mutation frequency is low in the population, the observed RR values can certainly be used.
with $S_0$ values taken from published information, such as Surveillance, Epidemiology, and End Results Program (SEER)\(^3\) cancer incidence tables (4), to calculate unbiased penetrance estimates for general populations.

Are risk factors overrepresented among case relatives? Empirically, breast cancer risks in relatives of population-based samples of case patients with ovarian cancer do not differ from risks in the general population. Our study observed a risk of breast cancer to age 70 years of 7.2% among first-degree relatives of ovarian cancer proband case patients not carrying BRCA1 or BRCA2 mutations and of 8.4% for all first-degree relatives (2). These frequencies are comparable to the 8%–9% figure seen in recent SEER data (4). None of the dozen cancer sites we examined had risks to family members that differed appreciably or statistically significantly from population risks (2,4). This fact suggests that risk factors (separate from BRCA1 and BRCA2 mutations) that might predispose to breast or other cancers are not overrepresented in patients with ovarian cancer (or that these risk factors do not cluster within families) and that our values for $S_0$ and penetrance are unbiased.

Begg identifies another potential bias in penetrance estimates, caused by associations between mutation status and genetic or familial risk factors. Potential confounding of RR estimates can happen in all observational studies, not just those that estimate penetrance. At present, there is little evidence for confounding in mutation RR estimates for breast cancer in relatives of patients with ovarian cancer. Ovarian and breast cancer essentially do not share nongenetic risk factors of any importance that can contribute appreciably to familial clustering (5). Some evidence for modification of BRCA1 and BRCA2 risks by polymorphic variation in other genes has been observed for breast cancer, but none—or if anything, an opposite pattern—has been observed for ovarian cancer (5).

Penetrance heterogeneity of specific BRCA1 and BRCA2 mutations is likely and would also constitute a heritable modifier of the risk for breast cancer. We observed a greater than fivefold increase in BRCA1-associated breast cancer risk for mutations in the 5' end of the gene compared with those in the 3' end of the gene (2). Begg (1) cited our null results for breast cancer associated with BRCA2 mutations overall, although we reported that penetrance was statistically significantly elevated for BRCA2 mutations outside the "ovarian-cancer cluster region" (nucleotides 4075–6503), about 50%, comparable to the penetrance of BRCA1 mutations as a whole (2). Other investigators have also found appreciable penetrance heterogeneity for specific BRCA1 and BRCA2 mutations (6,7). Penetrance of BRCA1 and BRCA2 mutations for ovarian cancer, however, does not show any of the same heterogeneity as for breast cancer (2). Thus, case probands with ovarian cancer are unlikely to overrepresent specific BRCA1 or BRCA2 mutations that could be associated with an excess risk of breast cancer.

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**REFERENCES**


**NOTES**

1 Editor's note: SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local non-profit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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Begg (1) recently pointed out limitations of estimating absolute risk from studies of case patients and their relatives. In particular, he points out that risk estimates from the case patients are likely to be inflated because risk coaggregates in the relatives of the case patients. The particular overestimation that he notes should be reduced if ascertainment corrections are used. It has been well noted in the genetic epidemiology literature that the sampling of families is a form of biased sampling. Methods to incorporate mutational information from some individuals and to simultaneously adjust for the ascertainment process have been available from standard statistical genetic software such as the Pedigree Analysis Package (http://hasstedt.genetics.utah.edu/download/pap50manual.pdf) or Mendel [Lange et al. (2)] but have not been widely used. Antoniou et al. (3) developed elegant adaptations of Mendel software to incorporate an ascertainment correction along with effects of additional genetic factors beyond BRCA1 and BRCA2. The statistical model they developed should adjust for biased sampling and so obtain reliable results, subject to the limited sample size of their study. As an alternative to the genetic epidemiologic approaches, which can be difficult to implement, standard cohort or newer kin–cohort approaches [Wacholder et al. (4)] have been applied. These approaches have the advantage of readily incorporating a broader range of survivorship modeling approaches than are available from genetic epidemiologic software, but their use may lead to biased results, as shown by Begg (1). Historical cohort approaches are valuable in genetic epidemiologic studies of cancer because they permit the study of multiple cancer outcomes.

An important issue not considered in the recent analysis by Begg is the effect
that underreporting of cancers can have on the risk estimates from a population-based study. The sensitivity of reporting of breast cancer in first-degree relatives of probands has varied among studies and ranges from 83% [Kerber et al. (5)] to 94% [Love et al. (6)]. The specificity of reporting of breast cancer in first-degree relatives has rarely been reported because of the difficulty in obtaining breast cancer information about individuals who have not been reported to have cancer. However, Anton-Culver et al. (7) found that reporting specificity was more than 99% in a very large study from a population-based registry. The sensitivity of reporting for other cancers is generally lower, as low as 0% for liver cancer [Love et al. (6)].

If we define the penetrance \( \phi \) to be the probability that an individual develops the disease (cancer), given that the person has a mutation (\( M \)), then we want to obtain \( \phi = P(D|M) \), where \( D \) is the event that a person has the disease and \( P \) denotes probability. Let \( \hat{\phi} \) represent the observed penetrance, \( \hat{D} \) represent the event that a person does not have the disease, and \( \hat{D} \) represent the event that a person is reported to have the disease. Ordinarily, the mutation status of the first-degree relatives of individuals is inferred. What we observe, in the absence of any corrections and by assuming the mutation status has been inferred in relatives, is

\[
\hat{\phi} = \frac{P(\hat{D}|M)}{P(D|M)} + \frac{P(\hat{D}|\hat{D},M)P(\hat{D}|M)}{P(D|M)} + \frac{P(\hat{D}|\hat{D})P(D|M)}{P(D|M)} \\
\cong \text{Sensitivity } P(D|M)
\]

The latter term is negligible because the false-positive rate is less than 1%. In the kin-cohort approach, the penetrance is approximately twice the risk for the relatives of the case patients who test positive for the mutation minus the risk for the relatives who test negative for the mutation [Wacholder et al. (4)], which leads to the estimated penetrance being attenuated by approximately the sensitivity in reporting of the disease in the relatives (as noted above). The population-based cohort studies reviewed by Begg (1) have not ensured that all cases of breast cancer have been reported by the probands. Thus, all of the cohort studies are likely to have underestimated, to some extent, the risks associated with carrying a mutation in BRCA1 and/or BRCA2. Family-based studies that include contact with multiple relatives are difficult to conduct but minimize concerns about reporting of cancers in relatives. Further development of models that accurately include estimates of underreporting of cancer are needed before population-based approaches can be accurately interpreted. Concerns about the sensitivity of reporting are even more important for evaluating results of other cancers that may be even less reliably reported than breast cancer.

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A recent article by Begg (1) discusses the published estimates of risks of cancer in women who carry a mutation in BRCA1 or BRCA2. Most estimates are based on studying the risks to relatives of women with breast or ovarian cancer who are known carriers. Begg argues that such estimates will be biased, in the sense that they do not reflect the average risks to all carriers in the population. This hypothesis would be correct if the cancer risks in carriers are modified by other genes (or other familial risk factors) or if some mutations confer higher risks than others. The existence of some familial risk modification appears likely (2), and there is some evidence for variation in risk by site and type of mutation (3). Under these circumstances, risk estimates from studies of carriers who have either a strong family history of breast cancer or have breast cancer themselves will, on average, be higher than risk estimates from studies of carriers without these characteristics.

However, the conclusions drawn by Begg have been interpreted by commentators as implying that the existing estimates of risk are grossly misleading and that one cannot draw any useful conclusions about the risks in women with a BRCA1 or BRCA2 mutation. For example, the Lancet reported that “The lifetime risk of developing breast cancer in individuals who have the BRCA1 and BRCA2 mutations might have been exaggerated in previous studies . . .” (4). Similarly, the British Medical Journal stated that “Many people—including some doctors—mistakenly believe that women who carry mutations in breast cancer genes BRCA1 and BRCA2 have a high risk of developing breast cancer” (5). Finally, the editorial that accompanied the Begg article in the Journal concluded that “…a widely applicable and meaningful estimate of penetrance is unlikely” (6). We believe that these interpretations are incorrect.

Perhaps the problem stems from a persistent use in the literature of the expression “the penetrance” [e.g., see (6)], as if there were a single entity that all studies are trying to estimate. Each study is estimating the average risk to carriers relevant to the subpopulation being studied (3). That these estimates might differ from one another does not invalidate them; rather, it gives new scientific information.

In practice, a counselor is rarely interested in the risks to the “average” carrier. Virtually all genetic testing is conducted on women in families with...
multiple cases of the disease—the types of families from which the original penetrance estimates were derived. Some women are tested on the basis of having weaker family histories or of having early-onset disease; risk estimates derived by studying the cancer incidence in relatives of population-based series of women with breast or ovarian cancer may then be more appropriate. Because one affected relative would usually represent an absolute minimum criterion for genetic testing, it seems unlikely that risk estimates that lie much outside this range will be needed in any practical situation.

We agree with Begg that risk estimates to carriers should, if possible, incorporate information on modifying factors. Indeed, a risk model along these lines to incorporate the effects of other genes that can predict risk in any type of family has now been developed (2). Studies of cancer risks in relatives of cancer patients will remain the primary source of data for deriving such models.

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Breast cancer risks in BRCA1 and BRCA2 gene mutation carriers may vary with other modifying genes or personal attributes. Begg (1) noted that such heterogeneity causes upward bias in risk estimates based on cancer occurrence in families of population-based samples of case patients with breast cancer. We argue that this bias is small compared with the standard errors of the estimates. Thus, the large variability in risk estimates across studies does not appear to be caused by their biases but rather by the large standard errors of their estimates. This assertion is supported both by the data reviewed by Begg and by our computer simulations, as we discuss below. Our simulations also show that estimates from multiple-case families are more precise than those from families of population-based case patients.

Table 1 shows results from the four studies reviewed by Begg that give estimates and 95% confidence intervals (CIs) for breast cancer risk among carriers of mutations in BRCA1 or BRCA2. The CIs are wide, reflecting the large standard errors of the risk estimates. We used the CIs in Table 1 to calculate a variance for each risk estimate in the table and then used the estimates and their variances to test for differences in risk across the three studies with data for each gene. We found no evidence that risk differs across studies, which does not support Begg’s hypothesis that some are more biased than others.

To investigate the relative magnitudes of bias and standard error in risk estimates from families of population-based samples of case patients with breast cancer, we generated data from 50 population-based synthetic studies. Each such study consisted of breast cancer data for the first-degree female relatives of 1600 population-based case patients with breast cancer who were typed for BRCA mutation status. To enrich the sample for carriers, we oversampled case patients with at least one affected first-degree relative. Specifically, we sampled case patients to obtain 800 with a family history of breast cancer and 800 without such a family history. We assumed various levels of heterogeneity in carrier risks from unmeasured genotypes of another modifying gene. We chose the parameters so that the mean risk by age 70 years among BRCA mutation carriers was 69%, regardless of the extent of heterogeneity among them. These findings, which are reported in detail elsewhere (6), provide surprising results about the extent of bias and standard error to be expected.

Table 2 shows three risk ranges among BRCA mutation carriers corresponding to three sets of assumptions about risk heterogeneity among carriers as a result of the modifying gene. The lower and upper risks in each range are, respectively, the risks among noncarriers.

Table 1. Population-based estimates and 95% confidence intervals (CIs) of breast cancer risk by age 70 years among carriers of BRCA1 and BRCA2 mutations

<table>
<thead>
<tr>
<th>Study</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Risk estimate, % (95% CI)</td>
<td>Risk estimate, % (95% CI)</td>
</tr>
<tr>
<td>Thorlacius et al. (2)</td>
<td>—</td>
<td>37 (22 to 54)</td>
</tr>
<tr>
<td>Anglian Group (3)</td>
<td>47 (5 to 82)</td>
<td>56 (5 to 80)</td>
</tr>
<tr>
<td>Antoniou et al. (4)</td>
<td>45 (22 to 76)</td>
<td>26 (14 to 50)</td>
</tr>
<tr>
<td>Satagopan et al. (5)</td>
<td>46 (31 to 80)</td>
<td>—</td>
</tr>
</tbody>
</table>

Table 2. Simulated breast cancer risk and 95% confidence intervals (CIs) by age 70 years in heterogeneous groups of BRCA mutation carriers

<table>
<thead>
<tr>
<th>Range of penetrances, %</th>
<th>Mean risk, %</th>
<th>Mean risk in first-degree relatives of carrier case patients, % (95% CI)*</th>
<th>Bias in first-degree relatives of carrier case patients†</th>
</tr>
</thead>
<tbody>
<tr>
<td>60–69</td>
<td>69</td>
<td>69.0 (57 to 81)</td>
<td>0</td>
</tr>
<tr>
<td>61–84</td>
<td>69</td>
<td>70.0 (57 to 83)</td>
<td>1.0</td>
</tr>
<tr>
<td>52–98</td>
<td>69</td>
<td>72.5 (57 to 88)</td>
<td>3.5</td>
</tr>
</tbody>
</table>

*Based on simulated data, as described in text.
†Using formula 2 of Begg (1) and the arguments of Wacholder (7).
ers and carriers of the modifying gene. We approximated the bias in mean risk among relatives of case patients as half of the bias given by formula 2 of Begg (1), based on the arguments of Wacholder et al. (7). We then used this approximation to calculate the mean risk among the relatives. The calculated bias is small. Even when BRCA mutation penetrances in the population range from 52% to 98%, the bias is only 3.5%. In contrast, the standard deviations of risk estimates across the 50 simulated studies were much larger, giving 95% CIs that span some 25–30 percentage points.

The results in Tables 1 and 2 indicate that the uncertainty in penetrance estimates obtained from families of population-based case patients substantially outweighs the bias. This uncertainty presents a formidable barrier to meaningful risk estimates as the basis for preventive decisions. Penetrance estimates obtained from multiple-case families ascertained in linkage studies or high-risk clinics also are biased upward. However, our simulations (6) suggest that this bias is no greater than that of population-based studies. More importantly, we found that the multiple-case families yield considerably more precise penetrance estimates than those obtained from population-based studies. The greater precision from multiple-case families reflects their greater number of BRCA mutation carriers per family. Thus, results from multiple-case families may be more informative than those from families of population-based case patients.

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RESPONSES

I am grateful to the correspondents for their interesting and insightful comments. Amos addresses two issues. First, he laments the fact that ascertainment corrections have not been widely used. However, available ascertainment adjustment techniques may have poor statistical properties in the context of risk heterogeneity. Standard ascertainment corrections use a conditional likelihood in which data from individual pedigrees are, in effect, weighted inversely by their probabilities of ascertainment. To be valid, these weights need to accurately reflect the impact of the unknown contributors to interindividual risk variation, but the information for making these inferences is contained in the patterns of breast cancer occurrence in the relatively few families with more than one occurrence of the disease. In the population-based setting, the preponderance of case probands will have no first-degree relatives with breast cancer and only a small proportion will have two or more (1). Any resulting inferences about the contributions of the unknown factors to the risk distribution may be highly model dependent, especially in the context of the small samples available for studying BRCA mutations, notwithstanding the encouraging simulation results reported recently by Epstein et al. (2) in a setting in which the model is fully specified and assumed known. Indeed, studies using high-risk families have consistently produced penetrance estimates that are much higher than those from the population-based studies, even with corrections for ascertainment. This fact provides empirical evidence of the inadequacy of available methods for ascertainment correction. More research is certainly needed on this topic.

Amos’s second point concerns errors in the reporting of family history of breast cancer. There is no question that we should be concerned about this issue, and efforts to verify the accuracy of reported information can only improve the validity of these kinds of studies. However, I am a little confused by his argument that misclassification errors must lead to a downward bias. He argues that overreporting can be effectively ignored because the false-positive rate is low. However, the vast majority (>90%) of family members are typically unaffected, and so the impact of false-positive errors on the total frequency of errors is proportionally larger than the impact of false-negative errors. Even if we assume that the false-positive rate is zero, the underestimation of penetrance in published population-based studies based on the false-negative rates quoted is only a small fraction of their discrepancy with the penetrances reported in the studies of high-risk families.

Risch and Narod argue that there is likely to be little bias in studies that use probands with ovarian cancer rather than breast cancer, such as in their study. They may well be correct. The relevant questions in this case are: 1) To what extent do breast and ovarian cancer cosegregate? and 2) Can mutations in BRCA1 and BRCA2 explain all of this association? Risch and Narod refer to the fact that the overall risk of breast cancer in the kindred of case probands with ovarian cancer in their own study was similar to Surveillance, Epidemiology, and End Results Program (SEER) rates of breast cancer. This observation seems a little surprising. Insight into the presence of common risk factors can also be gleaned by studying rates of second primary cancers (3). If we make use of data from SEER and eliminate all occurrences of second primary cancers up to 1 year after diagnosis of the first primary cancer, the standardized incidence ratio of breast cancer in women with a prior ovarian cancer is 1.5 (95% confidence interval [CI] = 1.3 to 1.6). Conversely, the standardized incidence ratio of ovarian cancer after breast
cancer is similar, at 1.6 (95% CI = 1.5 to 1.7). As indicated in the “Discussion” section of my article, these estimates are in the middle of the range of estimates that we would expect to be induced solely by BRCA1/BRCA2 mutations if the population prevalence of mutation is 0.1% and the (common) relative risks for breast and ovarian cancer are in the range of 10–20. Thus, on the basis of these admittedly highly approximate guesstimates, and recognizing that the impact of treatment of the first primary cancer may perturb these rates, the cosegregation of breast and ovarian cancer is plausibly explained by the common influence of BRCA1 and BRCA2 mutations.

Risch and Narod also make the interesting suggestion of adapting the kin–cohort methodology by anchoring the baseline incidence rates on the population rates rather than the rates observed in the kin–cohort and by using the observed data only to estimate the relative risks. They also cite evidence of penetrance heterogeneity between specific BRCA1 and BRCA2 mutations, an issue also mentioned by Pharoah et al.

Whitemore and Gong argue that the likely magnitude of the bias caused by risk heterogeneity is relatively small. They use as evidence hypothetical calculations of the bias induced by specific postulated degrees of risk variation. I have a minor quibble with them in that they calculate the bias in relatives rather than in probands. Although the kin–cohort calculations involve calculating the incidence in relatives, the penetrance estimators, including those of Wacholder et al. (4), adjust back to the probands, and so I believe that, for example, the bias in the third row of their Table 2 should more properly be reported as 7% rather than 3.5%. My more important concern is with their conclusion that “multiple-case families yield considerably more precise penetrance estimates than ... population-based studies.” Their logic is based on two arguments: the presumed low magnitude of bias caused by heterogeneity and the increased statistical power resulting from the higher numbers of events (i.e., breast cancer occurrences) in multiple-case families. Studies of high-risk families, or indeed any collection of families selectively obtained on the basis of observed outcomes, require correction for ascertainment bias, as indicated in the comments of Amos. That is, they must account for the fact that the occurrence of the multiple cases is the reason they appear in the statistical sample in the first place. If this correction is accomplished with full success and if there is no risk heterogeneity in gene carriers, then the penetrance estimates from high-risk families should be the same as those from population-based studies. In fact, the population-based studies have consistently demonstrated much lower estimates. I do not believe that wide confidence intervals are the reason for this disparity. It is caused by risk heterogeneity, by the failure of the statistical methods used to adequately correct for ascertainment, or by both. I suspect both.

Finally, I have only one comment on the interesting remarks of Pharoah et al. They state that virtually “all genetic testing is conducted on women in families with multiple cases of the disease ...” or others that have evidence of a high-risk phenotype. Although this observation may be largely true at the present time, the rapid development of the technology for genetic testing and its promotion by commercial interests may well result in its much broader application in the foreseeable future.


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REFERENCES


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1. Editor’s note: SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local non-profit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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We agree that Begg’s observations concerning the BRCA1 and/or BRCA2 (BRCA1/2) penetrance studies (1) have been misinterpreted by some commentators. Begg noted wide variation in population-based estimates of penetrance, and he further noted that many studies may have overestimated penetrance because they were based on families identified through a proband with cancer. This method could select for families with other risk factors that contribute to higher cancer penetrance for BRCA1 and BRCA2 gene mutations. This important observation points to the considerable uncertainty in our current understanding of the cancer risk associated with mutations in the BRCA1 and BRCA2 genes. However, it does not rule out a clinical role for BRCA1/2 mutation testing in some families.

The families most likely to benefit from BRCA1/2 mutation testing are those with a high prevalence of breast and ovarian cancer in a pattern consistent with autosomal dominant inheritance. An example is provided by the families used in the original linkage studies that led to the discovery of the BRCA1 and BRCA2 genes; these were families ascertained on the basis of multiple cases of breast and/or ovarian cancer, with at least some breast cancer cases occurring in men or in women at an early age (2–4). Initial and follow-up studies of cancer penetrance in these high-risk families indicate a lifetime risk for breast cancer of greater than 80% in female family members who inherited a mutation (2–4). Begg’s analysis suggests that this high penetrance may reflect the concurrent presence of two conditions: the gene mutation and one or more additional modifying factors that increase mutation penetrance. Alternatively, high penetrance could reflect the presence of specific BRCA1/2 mutations that are more penetrant than others. By either interpretation, unaffected women from
such families are likely to be at high personal risk for cancer if they inherit the mutation segregating in the family. Thus, the combination of pedigree data and mutation status can be used with confidence to estimate a high lifetime risk of cancer. Even in this setting, Begg’s analysis indicates the need for caution. In estimating high risk, we assume that any modifying factors promoting risk are shared by all family members at risk; however, sharing of modifying risk factors is likely to be incomplete and may explain why the cancer experience of different mutation carriers varies, even in high-risk families. For example, the age of onset of breast cancer and the likelihood of ovarian cancer appear to vary considerably, even among women from families ascertained on the basis of high rates of cancer (2,4–6). Nevertheless, clinicians can make a reasonable working assumption that the presence of a BRCA1/2 mutation in the setting of a high-risk pedigree indicates a substantially elevated risk for cancer and, thus, has value as a clinical test. Begg’s analysis also has implications for negative test results; clinicians should be cautious about concluding that a negative test result indicates an average cancer risk in women from high-risk families, because modifying factors promoting cancer risk may still be present in the absence of the segregating mutation.

More important, Begg’s analysis suggests the need for considerable caution in the use of BRCA1/2 testing when the inheritance of cancer in the family is more ambiguous. We believe the most prudent conclusion to be drawn from current data is that BRCA1/2 mutations elevate the risk of breast and ovarian cancer but that the degree of risk is difficult to quantify in the absence of other contributing data. Thus, we suggest that there is limited clinical value for BRCA1/2 testing in the absence of evidence for autosomal dominant inheritance of cancer risk in the family.

If specific modifying risk factors can be identified, it may be possible to develop more accurate risk estimates for individual patients with BRCA1/2 mutations and perhaps to develop interventions to reduce risk based on combinations of these factors and mutations. Ultimately, such research might allow us to specify evidence-based genetic testing recommendations, even in families without evidence for autosomal dominant inheritance of cancer risk. Much work remains to be done to achieve this goal, however, and the answers emerging from such research are likely to be complex. Our conclusion that “...a widely applicable and meaningful estimate of penetrance is unlikely” (7) reflects our expectation that more knowledge will lead to a better understanding of the variable cancer experience of women with BRCA1/2 mutations rather than to uniform penetrance estimates.

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