INVITED EDITORIAL
BRCA1 and *BRCA2* Testing: Weighing the Demand against the Benefits

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Mutations in the *BRCA1* and *BRCA2* genes in females confer strongly elevated risks of developing cancers of the breast and ovary. Ever since *BRCA1* and *BRCA2* were identified in 1994 and 1995, respectively, there has been a continuous debate as to whether (presymptomatic) testing for these mutations is beneficial, in clinical terms, and, if so, who should be eligible for testing (Collins 1996). Initial estimates of the gene frequency of *BRCA1* in the general population suggested that disease-causing mutations would be present in 1 in every 833 women (Ford et al. 1995). This prevalence represents the total mutational load in *BRCA1,* which we now know to consist of several hundred different DNA changes (Breast Cancer Information Core website). Together with the absence of an undisputed cancer prevention option for mutation carriers, such prevalence makes widespread population screening for these mutations not only unfeasible, but also undesirable. Accordingly, many advisory bodies, including the one under the auspices of the American Society for Clinical Oncology (ASCO Public Issues Committee 1996), have recommended that testing be restricted to women at high risk of developing breast or ovarian cancer. In general, such risk is indicated by a strong positive family history of one or both of these diseases.

However, with the discovery that several founder mutations in *BRCA1* and *BRCA2* occur at high frequencies in certain ethnic populations, the technical and financial limitations on such testing become less inhibitory. This is the case for the *BRCA1* mutations 185delAG and 5382insC, the *BRCA2* mutation 6174delT in the Ashkenazi Jewish population, and the *BRCA2* mutation 999del5 in the Icelandic population. Several anonymous surveys have indicated that slightly more than 2% of the Ashkenazim carry one of the three founder mutations (Struewing et al. 1995, 1997; Oddoux et al. 1996; Roa et al. 1996; Fodor et al. 1998). A rapid and sensitive assay for these mutations is already commercially available or easily designed at fairly low laboratory costs. Does this pave the way toward broad community-based screening among the Ashkenazi Jews for these mutations, not just among those clearly at greater risk as indicated by their family histories? The data presented by Hartge and coworkers (1999 [in this issue]) indicate that this is not so straightforward. These authors compared the results of anonymous genetic testing of the three *BRCA1/BRCA2* founder mutations in 5,318 Jewish men and women from the Washington, DC, area to personal and family histories of cancer as obtained from questionnaires completed by the participants. In all subgroups defined by age and cancer history, fewer mutations were found in this community sample than in clinical series studied to date.

If anywhere, the demand for testing is expected to be highest among individuals with a personal or family history of breast or ovarian cancer. What proportion of these individuals can be expected to carry a deleterious mutation in *BRCA1* or *BRCA2?* The Breast Cancer Linkage Consortium (BCLC) has estimated the risks of breast cancer conferred by *BRCA1* mutations to be ~50% by age 50 years and ~85% by age 70 years (Ford et al. 1994) (fig. 1). Combining this penetrance with the prevalence of the 185delAG mutation in *BRCA1* among Ashkenazi Jews, one can predict that ~19% of all individuals diagnosed with breast cancer by age 50 years, and ~9% of individuals diagnosed by age 70 years, are carriers of this mutation. Similar proportions are expected to carry the 6174delT in *BRCA2,* given its age-dependent penetrance (Ford et al. 1998) and prevalence rate (Oddoux et al. 1996; Roa et al. 1996). Up to 40% of all of Ashkenazi Jewish breast cancer patients aged <50 years could thus be carriers of either of the known founder mutations in *BRCA1* and *BRCA2,* providing a good rationale for broad testing. Yet Hartge et al. (1999) find only 9% of all patients with breast cancer (and 14% of patients aged <50 years) to carry the 185delAG, 5382insC, or 6174delT mutation—less than half the proportion predicted by the BCLC estimates. Nonetheless, their findings are supported by two earlier studies

Received February 8, 1999; accepted for publication February 18, 1999; electronically published March 12, 1999.

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This article represents the opinion of the author and has not been peer reviewed.

0002-9297/99/6404-0006$02.00

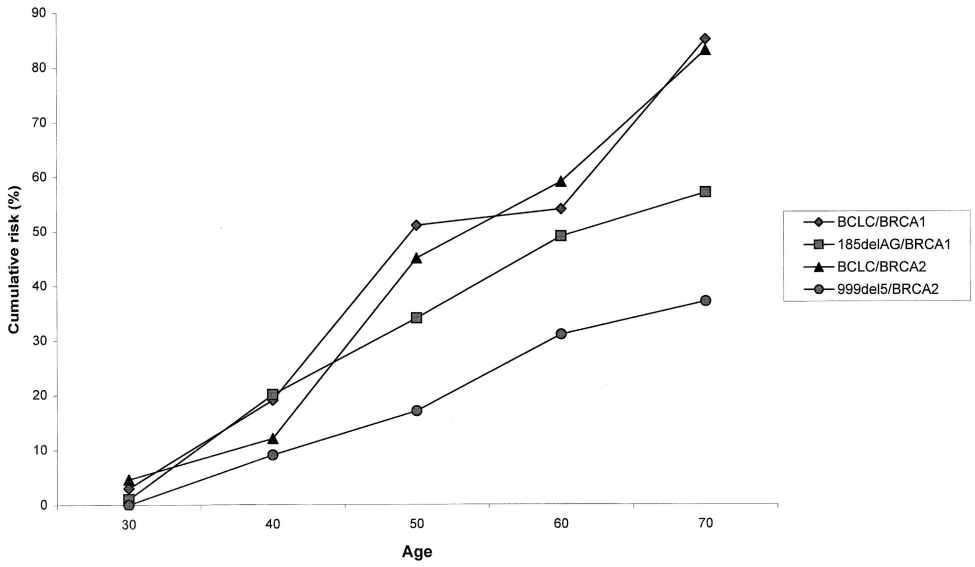

Figure 1 Comparison of cumulative breast cancer risk estimates conferred by *BRCA1* and *BRCA2*. The estimates of the Breast Cancer Linkage Consortium are taken from Ford et al. (1995; 1998), whereas those for the 185delAG mutation in *BRCA1* and the 999del5 mutation in *BRCA2* were taken from Struewing et al. (1997) and Thorlacius et al. (1998), respectively.

(Abeliovich et al. 1997; Fodor et al. 1998), that detected totals of 6.7% and 13.4%, respectively, among unselected patients with breast cancer (tables 1 and 2). Even studies selecting early-onset cases find fewer carriers than expected on this basis. How can this difference be explained? Hartge et al. (1999) were able to exclude lower overall prevalence rates for the three mutations in their particular study population, since the observed 2% accords very well with other studies of other Ashkenazi Jewish populations. More likely, the risk estimates derived by the BCLC are not applicable to the population studied by Hartge et al. (1999). Indeed, previous analysis of the same population survey estimated the cumulative breast cancer risk among the Washington, DC, Ashkenazi Jewish carriers at 33% by age 50 years and 56% by age 70 years (Struewing et al. 1997) (fig. 1). There were no significant differences between the estimates for the 185delAG, 5382insC, and 6174delT mutations. Although these estimates would already imply lower attributable risks associated with *BRCA1* and *BRCA2*, the observed breast cancer risk in noncarriers (13% by age 70) was also slightly higher than expected. Hence the "genetic burden" caused by *BRCA1/BRCA2* among patients with breast cancer diagnosed before age 70 years (i.e., the difference between genetic and nongenetic breast cancer) is in fact only 6% in this population.

A similar discrepancy between risk estimates of the BCLC and those derived from population studies was also seen for the *BRCA2* 999del5 mutation in the Icelandic population (Thorlacius et al. 1998). This mutation was found to confer a cumulative breast cancer risk of 37% by age 70 years, less than half of what was calculated by the BCLC (fig. 1). This highlights an important issue currently attracting much attention within the breast cancer genetics research community. The BCLC estimates derive from 237 families selected for having at least four cases of breast cancer and any number of ovarian cancer (Ford et al. 1998). It has been argued that this has caused a strong bias toward higher cumulative risk estimates. However, we should be cautious about dismissing the BCLC risk estimates on these grounds, for several reasons.

First, there are important methodological differences in the statistical analyses between the BCLC studies and the currently available population studies. The BCLC studies have used a LOD score method that maximizes the LOD score over a range of penetrances (Ford et al. 1994, 1998; Easton et al. 1995). This is independent of the type of mutation in the disease locus, since it requires linkage data for flanking markers (hence the selection of larger families, for the analysis to be informative). The genetic status of individual members of the families (affecteds and nonaffecteds alike) can be determined with great certainty. This is subsequently matched with clinical status, which, in most of the families under analysis, was often confirmed by histology or medical charts. Struewing et al. (1997) derive cancer risks by comparing the history of cancer among the first-degree relatives of carriers with that among the first-degree relatives of noncarriers. Cancer ascertainment in first-degree relatives relies almost entirely on interview of the index patient. Carrier status is determined only in screened individuals,

Table 1

Prevalence of *BRCA1* among Ashkenazi Jewish Breast Cancer Patients

Geographic Origin	Selection Criteria	Number Tested	Number Positive (%)	Reference
New York (Memorial Sloan-Kettering)	Age <42 years	80	16 (20)[a]	Offit et al. (1996)
Boston metropolitan area	Age 30–40 years	35	6 (17)[a]	FitzGerald et al. (1996)
New York metropolitan area	None	268	10 (3.7)[b]	Fodor et al. (1998)
Israel (Jerusalem)	None	178	16 (8.9)[b]	Abeliovich et al. (1997)
Washington, DC, area	None	288	15 (5.2)[b]	Hartge et al. (1999)

[a] 185delAG only.
[b] 185delAG and 5382insC combined.

on which basis one can estimate probabilities of disease among first-degree relatives. Hence, the relationship between disease and carrier status in first-degree relatives is less certain than in the linkage studies. (In the Icelandic study, data on cancer in first-degree relatives were available from the cancer registry, alleviating the cancer-ascertainment problem.) Furthermore, the outcome of this analysis in terms of *BRCA1/BRCA2*-conferred cancer risks is also inherently dependent on the overall cancer incidence in the control (noncarrier) population. As noted, the breast cancer risk in the community sample studied by Struewing et al. (1997) was already slightly higher than expected. Whether these methodological differences explain the differences in penetrance estimates is not clear at present, but it would be interesting to apply the LOD score method to a set of high-risk Ashkenazi Jewish families selected from the Washington, DC, area, for which all breast cancers are ascertained by chart analysis.

Second, besides the selection of "high-risk" families by the BCLC, additional fundamental differences with a community-based sample exist, which could influence the outcome of risk estimates. The BCLC studies have included families with a variety of different ethnic backgrounds—European, Icelandic, and North American. We can expect the mutational spectra of *BRCA1* and *BRCA2,* as well as the influence of environmental and genetic modifiers, to be more diverse among the families studied by the BCLC, compared with a single ethnic subgroup. Mutation-specific breast cancer risks like those reported for ovarian cancer (Gayther et al. 1995, 1997) could exist for *BRCA1* and *BRCA2*. The difference in overall breast cancer incidence between different populations is generally ascribed to differences in lifestyle or other environmental impact (Willett 1989), and studies analyzing the effect of such factors on *BRCA1/BRCA2*-conferred cancer risks are currently under way (Narod et al. 1995; Ursin et al. 1997; Brunet et al. 1998). Whether or not genetic modifiers of these risks actually exist is uncertain. This would require formal statistical analysis of *BRCA1*- or *BRCA2*-linked families for the presence of risk heterogeneity between families; such analyses have not yet been done for breast cancer. Yet some evidence has been obtained for a genetic modifier of the ovarian cancer risk caused by *BRCA1* (Phelan et al. 1996). It is conceivable that differences in allele frequencies at such loci exist between populations. Focusing on a population with a particular ethnic background could then draw out the effect of a specific interaction between a particular mutation and any of these modifying components. Clearly, the risks derived from population studies thus far concern specific *BRCA1* and *BRCA2* mutations and may not apply to carriers of other mutations. This underscores the importance of carrying out surveys in other populations, even though this involves a daunting amount of work relative to surveys in founder populations, because of the lower overall *BRCA1* and *BRCA2* prevalence.

Third, we should be aware that the same mutation could cause different cancer risks in different families, through modifying effects such as outlined above. If this is the case, population-based estimates might represent the average of considerable risk heterogeneity. Hartge et al. (1999) found 1.2% of all investigated subjects without a personal or family history of breast or ovarian cancer (~45 individuals) to be carriers of a *BRCA1* or *BRCA2* mutation. Of course, there may be errors in the reporting of cancers in relatives, and in some families, particularly smaller ones, there may be a deficit of potential female carriers. But this observation has been made by others as well (FitzGerald et al. 1996; Tonin et al. 1996; Abeliovich et al. 1997), and 45 such cases is quite a compelling number to suggest the existence of risk heterogeneity. Accordingly, the BCLC risk estimates could actually prove correct for a proportion of the families identified through population-based studies, whereas risks are much lower in others. Unless we learn more about the nature of the other factors that codetermine disease outcome in carriers, this poses a serious barrier to individual risk assessment.

The BCLC also analyzed the proportions of families with breast or ovarian cancer that could be attributed to either *BRCA1* or *BRCA2,* depending on the observed phenotypes as defined by the number of breast cancer

Table 2

Prevalence of *BRCA2* Among Breast Cancer Patients in Founder Populations

Population and Geographic Origin	Selection Criteria	Number Tested	Number Positive (%)	Reference
Icelandic:				
Population-based	None	459	39 (8.5)[a]	Johannesdottir et al. (1996)
Population-based	None	632	49 (7.7)[a]	Thorlacius et al. (1997)
Ashkenazim:				
New York (Memorial Sloan-Kettering)	Age <42 years	80	6 (7.5)[b]	Neuhausen et al. (1996)
Boston metropolitan area	Age <33 years	39	1 (2.6)[b]	Krainer et al. (1997)
Israel (Jerusalem)	None	178	8 (4.5)[b]	Abeliovich et al. (1997)
New York metropolitan area	None	268	8 (3.0)[b]	Fodor et al. (1998)
Washington, DC, area	None	288	11 (3.8)[b]	Hartge et al. (1999)

[a] 999del5.
[b] 6174delT.

cases diagnosed before the age of 60 years, and the number of ovarian cancer cases (Ford et al. 1998). This analysis showed that, for example, in 69% of all families with one case of ovarian cancer, the cases are due to *BRCA1*. Such figures can be used to estimate the prior probability that a woman is a *BRCA1/BRCA2* carrier on the basis of her family history of breast and/or ovarian cancer. However, many *BRCA1* and *BRCA2* mutation-screening studies of breast cancer and/or breast-ovarian cancer families have consistently produced fewer families with mutations than expected on the basis of the BCLC estimates (reviewed at the Breast Cancer Information Core website). This is explained partly by the inability of any mutation-screening technique to pick up all DNA changes in a gene. The most widely used screening modality (SSCP) still reaches a sensitivity of only 70%–80%, and even complete sequencing of all coding regions could miss substantial proportions of carriers, because it is PCR-based and would therefore miss large genomic rearrangements. But more importantly, the families analyzed by the BCLC certainly do not represent a typical cross-section of what is seen in cancer family clinics. Many studies have analyzed a set of clinic-based breast cancer families, often collected under much less stringent criteria than those used by the BCLC. Such a set more likely contains significant proportions of families either with a coincidental clustering of nongenetic (or "sporadic") breast cancer or with defects in genes other than *BRCA1* or *BRCA2*.

On the basis of observed population frequencies of specific mutations in *BRCA1* and *BRCA2,* one would have predicted these disturbing factors to be less significant in the Jewish population. Logistic regression models based on data from families ascertained through cancer genetic screening clinics predicted, for example, that ~40% of all probands with a family history of breast cancer only, and an average age at diagnosis of <40 years, are carrying one of the three founder mutations (Couch et al. 1997). Yet again, however, Hartge et al. (1999) find only 26% in this category, and an even more striking difference was observed when they compared their data with predictions derived from another study (Shattuck-Eidens et al. 1997).

Hartge et al. (1999) highlight several weaknesses in their study, which may help explain these differences. The survey did not constitute a random sample of the entire Jewish community; genetic testing was confined to the three known founder mutations, possibly neglecting others; and family history data were restricted to first-degree relationships, possibly missing a family history on the paternal side of the family. Yet these issues, important as they are and worthy of further research, do not interfere with the conclusion that the rationale for genetic testing among Ashkenazi Jews has become less apparent. Moreover, the issue of broad community testing is not only driven by the cost effectiveness of the test. As set forth above, important questions regarding individual risk assessment in the carriers still remain largely unanswered. Screening out those 9% carriers among all Jewish breast cancer patients will leave 91% testing negative, including quite a few with a significant family history of breast cancer. What are the psychological side effects of leaving them in uncertainty about their genetic risk? Or do we restrict screening to those diagnosed before the age of 40 years and accept that we will miss a number of carriers? This will need to be weighed against the clinical benefits of determining carrier status. The efficacy of breast cancer screening in premenopausal unaffected carriers is hedged with uncertainty too, while chemoprevention is still in the research phase. The acceptance of prophylactic mastectomy, the only intervention that effectively reduces breast cancer risks (Hartmann et al. 1999), may differ considerably from woman to woman. The data of Hartge et al. (1999) provide some useful estimates to warrant careful policy making in these areas.

Electronic-Database Information

URL for data in this article is as follows:

Breast Cancer Information Core, http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic/

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