

and in 9% (5/53) of cases with an affected first-degree relative, in a mutation screen covering between two-thirds and three-quarters of the coding regions of these two genes (Hopper et al. 1999, table 3).

Finally, the strong and highly significant effect that having had breast cancer has on the probability of being a mutation carrier could be used to derive an estimate of penetrance (i.e., age-specific cumulative risk of breast cancer), by using a case-control argument and appropriate population incidence rates and by taking into account the strong dependence of this effect on age, in which the odds ratio decreases from 10- to 2-fold across the four categories. In this regard, it is of interest that we found an average odds ratio of 9-fold for a set of protein-truncating mutations in BRCA1 and BRCA2 that cause early-onset breast cancer—and that this translates into a penetrance, until age 70 years, of just 40% when applied to Australian population rates (Hopper et al. 1999). Therefore, it is likely that a similar lifetime-penetrance estimate would apply to the founder mutations among U.S. Ashkenazi women, once the diminishing effect with age observed here has been counterbalanced by the ~30% higher underlying rates in the United States compared with Australia. Thus, population-based data on mutation carriers, such as those provided in some detail by Hartge and colleagues, are providing a new perspective on how genetic factors are evident in common diseases, challenging previous beliefs and language based on "monogenic" diseases (see Hopper et al. 1999).

JOHN L. HOPPER AND MARK A. JENKINS  
*Centre for Genetic Epidemiology, The University  
of Melbourne, Carlton, Victoria, Australia*

### Electronic-Database Information

Accession numbers and URL for data in this article are as follows:

Online Mendelian Inheritance in Man (OMIM), <http://www.ncbi.nlm.nih.gov/Omim> (for BRCA1 [MIM 113705] and BRCA2 [MIM 600185])

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Address for correspondence and reprints: Dr. J. L. Hopper, The University of Melbourne, Centre for Genetic Epidemiology, 200 Berkeley Street, Carlton, Victoria 3053, Australia. E-mail: [j.hopper@gpph.unimelb.edu.au](mailto:j.hopper@gpph.unimelb.edu.au)

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### Response to the Letters from Hopper and Jenkins and Foulkes et al.

*To the Editor:*

These two thoughtful letters (Hopper and Jenkins 1999 [in this issue]; Foulkes et al. 1999 [in this issue]) illustrate some of the difficulties in drawing conclusions from the current body of data: even in very large studies, the number of subjects with breast or ovarian cancer in their families is small enough that different statistical models can yield quite different assessments of how likely a person is to be a mutation carrier. When the penetrance function has been securely established, probably the best model will be based on genetic inheritance (Berry et al. 1997) rather than on classification and regression trees (CART) (Breiman et al. 1984), multiple logistic regression (MLgR), or multiple linear regression (MLnR) (Wacholder 1986). We elected to explore the data with

