Letters to the Editor

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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 CART, to build an "agnostic" model, close to the data, and added MLnR to try to separate the effects of various factors (Hartge et al. 1999). We chose not to use MLgR, to avoid distortion where data are sparse but projections are clinically relevant. For example, although the figure in the letter by Hopper et al. (1999) offers a clear qualitative depiction of the important factors, we caution that points on the graph depend heavily on choice of statistical model.

A word about MLgR: it can seriously misrepresent the data if the model is misspecified. Although MLgR is well suited to most problems in cancer epidemiology, in which the probability of disease developing is low for all exposure categories, it is not well suited here, where the probability of being a carrier, given personal and family history, can range from ~0% to ⩾20%. Under MLgR, an effect with an odds ratio of 2 raises the baseline risk of being a carrier, from 0.1% or 1% to ~0.2% or 2% but from 10% or 50% to ~18% or ~67%. Only with relatively high baseline risk would an odds ratio of 2 be an important factor in an individual's decision-making process.

The central conclusion from our volunteers remains that the carrier probabilities in those individuals with family history of breast or ovarian cancer are substantially lower than indicated by early published estimates.

SHOLOM WACHOLDER AND PATRICIA HARTGE
Division of Cancer Epidemiology and Genetics
National Cancer Institute
Bethesda

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Address for correspondence and reprints: Dr. Sholom Wacholder, Division of Cancer Epidemiology and Genetics, National Cancer Institute, EPS 8046, Bethesda, MD 20892-7244. E-mail: Wacholder@NIH.GOV

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