Re: Validation of the Gail et al. Model for Predicting Individual Breast Cancer Risk

We would like to clarify an issue arising from the article by Spiegelman et al. (1) and their reference to data from our study (2). The authors referenced data in their discussion from an abstract by Vogel et al. (3). It is important to note that the published abstract, although based on the same data set as Bondy et al., does not include any of the data discussed by Spiegelman et al. and were obtained by personal communication from Vogel. Furthermore, the cited abstract is from a presentation at the 1993 annual meeting of the American Society of Clinical Oncology and contains an error that was corrected from the podium by Vogel. The error in the abstract was the number of observed (O)-to-expected (E) cancers reported (O/E = 0.49; 95% confidence interval = 0.35-0.67). The correct observed to expected number of cancers was 1.01 as stated in our report.

We would like to alert the reader to reference our report (2) and not the incorrectly cited abstract (3). We hope this correspondence clarifies the issues.

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References


Note

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The model following the standard form given by the first two equations in Gail et al. [(5), p. 601] explains 83% of the cases observed in the Nurses’ Health Study, but only 41% of the cases are attributable to risk factors included in this model, while age alone explains 71% of the cases. These calculations were obtained using the formula for the population attributable risk percent (PAR%) (see equation box on next page) (6), where RRIj...p is the risk estimated in the Nurses’ Health Study with a model of the same form as Gail et al. [(5), p. 601, Table 4], relative to the lowest observed risk category, and P(R|GEMEN = i, NB1OPS = j, ..., D = 1) is the proportion of cases with the given combination of model risk factors. It should be noted, however, that the accuracy of PAR% calculations is limited by the accuracy of the model that provided the estimated RRs. Since the Gail et al. model gives somewhat higher RRs for the same risk categories, the
PAR% obtained from the RR's given by Gail et al. are somewhat higher: 85% of the cases observed in the Nurses' Health Study are explained, and 47% are attributable to risk factors included in the model. Using the same model and estimated RR's, Gail et al. estimated an identical PAR% for model risk factors using the Breast Cancer Detection Demonstration Project study population (7).

From these calculations, we conclude that most of the differences among women's risk of breast cancer can be attributed merely to differences in their ages rather than to the currently known risk factors. With this limitation, it is debatable whether this or another similar model is useful for individual case prediction. More detailed mathematical modeling more closely connected to our knowledge of the biology of breast cancer as presented by Rosner et al. (8) and work in progress by the same authors may be able to supply us with more accurate models for individual case prediction than available through these standard multiplicative modeling techniques. Nevertheless, we urge caution in promoting these models for individual case prediction in the absence of safe and effective methods for primary or even secondary prevention of the disease. Challenging statistical issues need to be resolved and valid methods need to be developed for assessing the accuracy of and expressing the uncertainty in individual prediction of binary outcomes, such as receiving a breast cancer diagnosis over the course of a lifetime, in order to assist individual decision-making.

We wish to point out that data discussed on p. 605 of our article (5) were incorrectly referenced to an abstract by Vogel et al. The correct reference is a personal communication from V. Vogel. These data subsequently appeared in expanded form in a paper by Bondy et al. (9) in the same issue of the Journal as our article.

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References

(6) Miettinen OS: Proportion of disease caused or prevented by a given exposure, trait or intervention. Am J Epidemiol 99:325-332, 1974

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Dr. Atkins comments that a cohort study provides a more "firmly based evidence of association" than a case-control study. This may be true when either: 1) the base population from which controls are sampled is not well defined (as in hospital-based case-control studies), or 2) the exposures and other covariates are difficult to measure in retrospect.

As regards the first point, the Breast Cancer Detection Demonstration Project (BCDDP) base population is a well-defined cohort from which matched controls were randomly sampled. Therefore, the inference is soundly based (1,2).

As Dr. Atkins suggests, one might expect that the quality of data would be better in a cohort study than a case-control study. Indeed, the Nurses' Health Study (NHS) had a number of strengths, including the fact that the rates of response to questionnaires were very high. However, the BCDDP studies had the advantage that data were elicited by trained interviewers, rather than by mailed questionnaires. Moreover, even though the NHS subjects were followed prospectively, the data were elicited by an appeal to memory. At base line in 1976, women were asked about age at menarche and age at first live birth. Except for the remote possibility of differential recall bias, it would seem that appeals to the memory of case patients and control subjects in the BCDDP would yield information of similar quality. Changing covariates, such as number of affected first-degree relatives and number of previous breast biopsies, were obtained from repeated mailed questionnaires in the NHS and from personal interviews of case patients and matched control subjects in the BCDDP. There was a potential for differential recall bias not only in the BCDDP but also in the NHS because subjects in the NHS provided information on disease status and on changing covariates in the follow-up questionnaires.

Dr. Atkins urges Spiegelman et al. (3) to develop a model for absolute risk. In fact, the Poisson model given by Spiegelman et al. can be used for this purpose. However, we would be reluc-