

Note

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Response

Thanks to Dr. Schaid for his letter. We agree that many of the calculations in (1) can also be performed using LINKAGE. The approach in our article was pedagogical and limited to easier mathematics. We advertised that our program makes more general calculations and, as Dr. Schaid points out, our group (Parmigiani G, Berry DA, Aguilar O: unpublished manuscript [www.isds.duke.edu]) extends the model described in (1) to the simultaneous consideration of BRCA1 and BRCA2. Our program gives the probability of a mutation at BRCA1 and also the probability of a mutation at BRCA2, while LINKAGE and other standard software can consider only one breast-ovarian cancer gene. In view of the differing penetrances for these two genes, the ability to consider both genes is important, and Dr. Schaid would seem to agree that it is important. The alternative of using standard software and ignoring the differences in penetrances for BRCA1 and BRCA2 can give misleading answers.

Dr. Schaid raises two additional methodologic points. First, when we know only that an individual was diagnosed with cancer over some range of ages, we suggest giving probabilities for the two end points of the interval. Dr. Schaid prefers conditioning on the available information and reporting a single number. This is an attractive alternative and a straightforward modification of our software. We will introduce it in future versions, perhaps as an option to the user. Giving an interval, however, has an important advantage. It indicates to the counselland that better information would allow for a more accurate answer. In addition, it conveys a sense of the uncertainty resulting from vagueness in the family history information.

Second, Dr. Schaid indicates that our program does not handle third-degree relatives. The conceptual framework laid out in (1) lends itself to a direct extension, which we plan to carry out. We agree that, in some circumstances, reliable information about great-grandparents and cousins helps in assessing genetic risk. However, we do not share Dr. Schaid’s optimism about the importance of third-degree relatives in practical counseling situations. People usually know little about the history of cancer of their third-degree relatives. And, what they do know is usually biased. For example, if cousin A had cancer but cousin B did not, then one is more likely to remember A and one might even forget that B exists. Members of an obvious ‘cancer family’ will usually know more about their third-degree relatives than do the rest of us, but even cancer-family members will have a hard time with ages at diagnosis. Also, in a family with many cases of cancer, one’s third-degree relatives do not add very much information to one’s first- and second-degree relatives, even if the circumstances of one’s third-degree relatives were precisely known.

We thank Dr. Schaid for his interest in our approach and in our software. His comments will help us provide better tools for individualized counseling and informed decision making about genetic testing. The program described in our unpublished manuscript, which considers both BRCA1 and BRCA2 mutations, is available free of charge to noncommercial users interested in scientific research and genetic counseling. The user needs only input the family’s history and whether the family is Ashkenazi Jewish but does not have to input the incidences by age and disease for each gene, as when using standard software. A UNIX version can be obtained by sending e-mail to gp@isds.duke.edu (Giovanni Parmigiani). A WINDOWS 95 and NT version is also available.

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Re: Multiple Neoplasias: an Oncologic Reality

Two recent interesting letters (1,2) focused on multiple primary neoplasias. Prados et al. (1) reported a patient who developed five neoplasms and Decher et al. (2) described seven patients with five or more cancers. The interest of the authors was not to describe freaks of nature, as Prados et al. stated, but to evaluate the risk of developing further independent neoplasms in subjects affected by one primary cancer.

These letters described patients with an unusually high number of tumors. However, the relationship between the number of cancers that can be attributed to a patient and the rules adopted for multiple primary neoplasias definition should be raised.

The classification of multiple primary neoplasias is still an open issue. The International Agency for Research on Cancer (IARC) has developed a classification, recently modified (3), which is widely used, at least by cancer registries. Nevertheless, in the sixth volume of Cancer Incidence in Five Continents (4), about 60% of the population-based contributing registries adopted rules on multiple primary neoplasias coding that differed, to some extent, from the IARC (4).

Prados et al. defined multiple primary neoplasias according to criteria similar to the IARC classification: different organs, different morphologies, and metastases ruled out. Therefore, the number of tumors to be attributed to Prados’s patient would not change by use of the IARC classification. Decher et al. did not state which rules they adopted, but, certainly, they did not follow the IARC. The patients in their paper had a mean of 5.57 cancers, but they would have a mean of 3.86 cancers (including three in situ tumors) according to the IARC rules. Thus, the number of can-
cancers would decrease by more than 30%. Naturally, this calculation does not confer any benefit on the patients of Decher et al. but shows the effect of different classifications on the number of multiple primary neoplasias. In our experience with 300 cancer patients, the number of multiple primary neoplasias fluctuated from 240 to 254 according to different classifications used in Italy (5). Similar findings occurred in another international cooperative study (6). Both studies, however, evidenced a very high agreement when the IARC rules were used.

These results stress the importance for comparative purposes, between registries but also between clinical series, of using the same multiple primary neoplasias classification (7).

Among others, the IARC classification is widely diffused, its rules are relatively simple to apply and conservative (7), and it has shown to have a very good reproducibility (5,6).

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Responses

Multiple neoplasias are a clinical reality. The causes are numerous, such as previous chemotherapy and radiotherapy for other malignant tumors, tobacco use, familial syndromes, or possibly diet (1–3).

The purpose of our letter was not to describe freaks of nature but to emphasize that the occurrences of multiple neoplasias in the same patient are becoming more frequent.

We agree with Crocetti and Buiatti that a common classification of multiple neoplasias should be adopted to allow for comparisons among studies.

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Crocetti and Buiatti raise an interesting issue with respect to the classification of multiple primary tumors. The Upper Midwest Oncology Registry (SEER) classifies multiple primaries according to the Surveillance, Epidemiology, and End Results (SEER) recommendations as described in the Standards of the Commission on Cancer (1). SEER classification has been the standard in the United States since 1973 and precedes the International Agency for Research on Cancer (IARC) guidelines. Within the United States, SEER data are widely used to ascertain comparability. Primary cancers classified according to SEER rules can be converted using IARC rules, because the SEER classification is more detailed than the IARC. WC have reclassified the multiple primaries of our original seven patients according to IARC rules as published in 1991 (2). We were unable to obtain a copy of the internal report mentioned by Crocetti and Buiatti that may contain modified rules. By IARC rules, four of the seven patients had five or more primary cancers, and one patient had four primary cancers. The two additional patients had one and two primary cancers, respectively. The difference between the SEER and IARC categorization is due to IARC counting multiple colon cancers in the same person as a single primary cancer. Here is a list of the original patients, the total number of primary cancers using IARC rules, and a list of primary sites.

Patient 1: five primary cancers—kidney, sigmoid colon, renal pelvis, supraglottis, and prostate gland

Patient 2: five primary cancers—uterus, renal pelvis, ascending colon, rectum, and upper lobe of the lung

Patient 3: six primary cancers—two in renal pelvis (one adenocarcinoma, one squamous), lung, ureter, bladder, and prostate

Patient 4: one primary cancer—two in cecum and three in colon

Patient 5: two primary cancers—rectosigmoid junction, four in colon

Patient 6: five primary cancers—lymph nodes of head, neck, face; cecum, labium majus, rectum, breast

Patient 7: four primary cancers—breast, thyroid, rectum, and two adenocarcinomas in colon

In summary, comparison of data within the United States requires the use of SEER rules because of the large number of years of data collected using this classification system. The authors recognize that future documents should contain both SEER and IARC classifications to enable both the United States