Re: Characterization of Hereditary Nonpolyposis Colorectal Cancer Families From a Population-Based Series of Cases

For cancer prevention and research, it is important to have accurate knowledge of the frequency of specific syndromes. Population-based studies can be valuable tools in obtaining such data because they avoid selection bias. The study by Peel et al. (1) was a welcome attempt to quantify the proportion of hereditary nonpolyposis colorectal cancer (HNPCC) on the basis of the Amsterdam criteria. These criteria require that at least three family members be ascertained with colorectal cancer and that one of these patients be a first-degree relative of the other two (i.e., an affected parent and two affected offspring, two affected siblings and one with an affected offspring, or three affected generations). The criteria have been criticized because they depend on family size (2). If the average family size is shrinking in a population, the apparent proportion of so-defined HNPCC is bound to become smaller (2). Nuclear families with three or more affected individuals are rare in current Western populations. For example, the Swedish Family-Cancer Database with 2.1 million nuclear families contains only some 20 families (0.001%), where one parent and two or more offspring present with colorectal cancer (3). This implies that most HNPCC families fulfilling the Amsterdam criteria depend on second-degree relations. If grandparents are included then, on average, colorectal cancers in these families are diagnosed in the course of some 50 or more years—e.g., a grandchild in the 1990s, a child in the 1960s, and a parent in the 1930s. The major problem is how the HNPCC-related cancers from the early part of the last century are ascertained.

Glanz et al. (4) carried out a questionnaire study of familial colorectal cancer in Hawaii, asking probands to identify colorectal cancers among the first-degree relatives. Despite a medically confirmed diagnosis, 25% of the probands failed to report colorectal cancer in offspring or siblings. Such false reporting of cancers in family members is known from other studies as well [see (4)]. Any false reporting has severe consequences for the application of the Amsterdam criteria. If the reporting of cancer in one sibling is correct with the probability of 0.75, then the probability of having two first-degree relatives correctly reported is 0.56. Moreover, underreporting is not the only problem; false-positive reporting is also likely (5). No doubt, reporting of cancers from a second-degree relative is even worse, and most families fulfilling the Amsterdam criteria include such relations. It is likely that the reporting is more accurate in a clinical study, where the patient has had many visits and is often assisted by a relative. The study by Peel et al. (1) was carried out as a telephone interview, and the report gives no indication whether any measures were taken to confirm the reported cases of colorectal cancer in the families, particularly among second-degree relatives. Unless some confirmation is available, the figures on the population proportion of HNPCC and the apparently high proportion of proximal cancers remain speculative.

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RESPONSE

Our recent report described a preliminary characterization of hereditary nonpolyposis colorectal cancer (HNPCC) families from a population-based series of colorectal cancer probands. We attempted to estimate the proportion of HNPCC cases that are seen in a large population-based colorectal cancer series from a heterogeneous population. In doing this, the most accurate way of proceeding would have been to undertake a full molecular characterization of all of the colorectal cancer probands in the study (1134). However, this would have been impractical given present resources. In the absence of such a molecular characterization of the disease in all probands, an initial characterization based on family history data followed by molecular characterization of selected cases seemed to be appropriate. The Amsterdam criteria we adopted represent a widely used set of standards enabling comparisons to be made with other studies. We recognize the limitations of the Amsterdam criteria as mentioned by this letter and, indeed, in our report, we mention an additional 83 probands that may be included as possible HNPCC kindreds based on less-restrictive family history criteria such as the Bethesda guidelines.

Family history data were collected based on 1) a preliminary telephone interview followed by 2) mailed information collected during the telephone interview, so that the proband was able to verify the data with family members, then 3) telephone or in-person follow-up interview(s) with family members to
obtain a release of information for pathology verification in those affected and self-verification of the absence of cancer in those who were unaffected. Verification consisted of pathology reports, cancer registry reports, family-member and self-verification, and death certificates. It is likely that false reporting and underreporting contributed to errors in the final figures for population levels, but errors of this type are unavoidable in such large-scale studies. Moreover, problems of this sort should be fairly equivalent across the whole cohort and may actually underestimate the total number of HNPCC cases. Comparisons within the study may be more valid given that data were collected in the same way for all participants. Thus, any findings between the different HNPCC, familial, and sporadic groups may be more valid in this study, such as the finding that a higher proportion of cancers occur in the rectum and rectosigmoid areas rather than in proximal areas as suggested in the letter.

We hope that further study of this population-based colorectal cancer cohort using an approach combining family history analysis and molecular characterization will give us more definite knowledge of the frequency of the HNPCC syndrome.

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