CLINICAL–ALIMENTARY TRACT

Cancer Risk in Hereditary Nonpolyposis Colorectal Cancer Syndrome: Later Age of Onset

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Background & Aims: **Mutations in the mismatch repair genes cause hereditary nonpolyposis colorectal cancer (HNPCC) syndrome and convey high lifetime cancer risks for colorectal (CRC) and endometrial cancer. Currently, cancer risks for individuals with HNPCC are based on data from clinically ascertained families. The purpose of this study was to re-examine the penetrance in HNPCC using a comprehensive dataset from a geographically defined region.** ***Methods:*** **A combined dataset of 70 HNPCC families ascertained by traditional high-risk criteria and by molecular screening comprising 88 probands and 373 mutation-positive family members was used. Statistical methods were modified survival analysis techniques.** ***Results:*** **In mutation-positive relatives (excluding probands), the median age at diagnosis of CRC was 61.2 years (confidence interval [CI], 56.3–68.0 y). The lifetime risk for CRC was 68.7% (CI, 58.6%–78.9%) for men and 52.2% (CI, 37.6%–66.9%) for women. Considering only probands, the median age at diagnosis of CRC was 44.0 years (CI, 41.0–46.3 y). Median age of onset of EC was 62.0 years (CI, 55.9 y to an upper limit too high to calculate) with a lifetime cancer risk of 54% (CI, 41.9%–66.1%).** ***Conclusions:*** **A markedly later age of onset for CRC at 61 y than previously reported (~44 y) is suggested, resulting mainly from a more rigorous method of analysis in which all gene-positive individuals (both affected and unaffected with cancer) are considered. Lifetime cancer risks may be lower for CRC and endometrial cancer than presently assumed. If confirmed, these data suggest a need to alter counseling practices, and to consider HNPCC in older individuals than before.**

Determining the penetrance of gene mutations predisposing to cancer is important because of its impact on the counseling and surveillance of mutation carriers. For instance, hereditary nonpolyposis colorectal cancer (HNPCC), also known as *Lynch syndrome*, is characterized by a strong predisposition to colorectal and endometrial cancer and by a weaker predisposition to cancers in many other organs.[1–3] Cancer surveillance guidelines generally are based on the reported age-specific risks for these cancers and may need to be altered if these risks have been overestimated. In addition, accurate penetrance figures affect the way in which we diagnose HNPCC. Because molecular testing to identify gene mutations is both work-intensive and expensive, risk assessment criteria have been developed to determine which patients should be tested for HNPCC.[4–7] Most of these criteria include an age criterion, restricting testing to those diagnosed with colorectal cancer (CRC) under a certain age. Thus, if the average age at diagnosis of CRC is later than has been reported previously, these screening criteria may need to be revised.

Estimates of HNPCC gene penetrance (lifetime cancer risk) for mutation-positive individuals have proven difficult to determine and could be dependent heavily on the source of the reference sample.[8–10] In particular, unmeasured genetic or environmental factors and ascertainment effects could produce higher lifetime risk (LTR) estimates for persons from multiple-case families than for those ascertained through population screening or screening of large samples of affected patients. Moreover, LTRs obviously are inflated if only individuals already diagnosed with cancer are included in the analyses.

A well-publicized example of how ascertainment affects penetrance estimates comes from studies of carriers of the

Abbreviations used in this paper: CRC, colorectal cancer; HNPCC, hereditary nonpolyposis colorectal cancer; LTR, lifetime risk.

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BRCA1 and *BRCA2* mutations that are common among Ashkenazi Jews. It was shown that penetrance appeared to be much higher in families identified through multiple cases[11] than in families identified through population-based molecular screening.[12,13] However, the issue is controversial with a recent report that provides evidence supporting an opposing hypothesis among relatives of an unselected series of breast cancer cases.[14]

Numerous studies have addressed the LTR and age of onset of HNPCC-associated cancers but all are based on clinically ascertained high-risk families.[1,15] With few exceptions[1,16] to date, the mutation status of the individuals either was not known or was known only partially. In this study we determine ages of onset and LTRs in known carriers of mismatch repair gene mutations irrespective of cancer status ascertained from a defined geographic region. Ascertainment was both by traditional high-risk criteria and by molecular screening of consecutively diagnosed CRC patients unselected for risk criteria.

Materials and Methods

Cohort 1

Cohort 1 consisted of members from 45 HNPCC families in whom a germline mutation of *MLH1* (N = 42) or *MSH2* (N = 3) had been detected. The probands presented with CRC. They were accrued over a period of 15 years between 1980 and 1994 by 2 surgeons based on clinical data and family history. The patients came from a defined geographic area in southern and southeastern Finland. Their mutation status was determined by molecular genetic testing beginning in 1994. Of note, the ascertainment of most of the probands occurred before the first set of criteria for the diagnosis of HNPCC[4] had been formulated. However, the inclusion criteria were young age of onset, family history of colon cancer, and proximal location of the colon tumor. Thus, ascertainment of these probands did not differ essentially from the way ascertainment generally is practiced today in a high-risk clinic setting. Family members of the probands were identified systematically by using a combination of the inclusive population and cancer registries that exist in Finland. Probands and family members from cohort 1 were removed from data analysis if (1) they also appeared in cohort 2, (2) their mutation status was unknown, or (3) their diagnosis data were incomplete. The number of mutation-positive probands used for the analysis in these pedigrees was 59 (29 men). Included in the data analysis were 218 relatives (111 men) who tested mutation positive or were obligate mutation carriers. For further information on this cohort including a description of the mutations see the article by Aarnio et al.[16]

Cohort 2

Cohort 2 consisted of members from 25 HNPCC families in whom a germline mutation of *MLH1* (N = 23) or *MSH2* (N = 2) had been detected. The probands presented with CRC. The accrual was population-based using microsatellite instability testing of the colorectal tumor as the primary screening method. Briefly, all patients with colorectal adenocarcinoma diagnosed during a 4-year period from 1994 to 1998 at 9 regional tertiary-care hospitals in southern and southeastern Finland were eligible. Accrual was independent of age, family history, and clinical characteristics. Patients accrued to the study represented approximately 65% of all CRC cases in this geographic region. Among a total of 1044 patients accrued to the study there were 128 patients with microsatellite-unstable tumors. Sequencing of genomic DNA in these individuals disclosed 29 probands (19 men, 10 women) with a mutation. As in cohort 1, by linking the population and cancer registries of Finland, inclusive pedigrees were drawn of the 29 probands' families. This resulted in a total of 25 pedigrees (families) because 3 families had more than 1 proband. As in cohort 1, at-risk family members were offered genetic testing. Among the relatives, 155 (79 men) tested positive for the mutation or were obligate mutation carriers. Here we present data on these 29 probands and 155 relatives. Further information about this cohort, including a description of the mutations is provided elsewhere.[17,18]

Definition of the Study Population

For the purpose of determining the LTR and age at onset the mutation-positive family members (excluding probands) from cohorts 1 and 2 were combined. For the purpose of comparing age at diagnosis of probands, cohorts 1 and 2 were analyzed separately.

Statistical Considerations

Even if LTR estimates from population-based gene-positive cohorts are of the same magnitude as those from multiple-case families, there remains the possibility of systematic differences in the age of onset. We investigated differences in age of onset medians and means between our combined dataset (representing samples resulting from the 2 modes of population screening) and in published reports from studies of high-risk families.

Only relatives, not probands, were included in our principal analysis for estimation of LTR because probands contribute an LTR of 100%, which would result in an upward bias in the estimate for relatives. A similar distortion will occur in series in which most or all mutation-positive individuals considered are those already diagnosed with cancer. We used a modified form of survival analysis[19] that identifies the onset of disease as the principal decrement and mortality from competing causes as withdrawal. With this technique a person contributed information to the analysis for as long as he/she was followed-up, whether or not cancer occurred. For example, a gene-positive man who never developed colon cancer and died at age 60 still would contribute 60 years of follow-up evaluation to this analysis. This technique is more rigorous than the naive approach of taking the means of only those with cancer. It should be noted that in this analysis a contributor to data loss was that