Frequency of Hereditary Nonpolyposis Colorectal Cancer

A Prospective Multicenter Study in Finland

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PURPOSE: Hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominant cancer syndrome characterized by early onset of colorectal carcinomas (CRC). Recently, two HNPCC genes have been mapped and cloned, one in the short arm of chromosome 2 and another in the short arm of chromosome 3. There has been a major controversy about the frequency of HNPCC. The few estimates available have been based on series selected by age or series representing local area. The purpose of the present study was to design a nonselected, prospective, multicenter study, taking into account the family background and other risk factors of CRC. METHODS: The proportion of HNPCC of all (N = 406) CRC cases was evaluated in a prospective multicenter study. Family history and other risk factors were investigated over a 12-month period for all new CRC patients in ten hospitals. These cases constituted 23 percent of all CRCs diagnosed in Finland during the study period. RESULTS: Three (0.7 percent) cases of verified and seven (1.7 percent) cases of suspected HNPCC were identified, following the evaluation of all families with features indicative of susceptibility to cancer. The proportion of identifiable risk factors of CRC was 5.8–7.5 percent (HNPCC, 0.7–2.4 percent; previous CRC, 3.4 percent; ulcerative colitis, 1.0 percent; familial adenomatous polyposis coli, 0.7 percent). CONCLUSION. This prospective multicenter study revealed that the frequency of hereditary colorectal cancer is lower than in some previous studies, when diagnosis is based on extensive pedigree analysis. This result with recent findings of common ancestral founding mutation in Finnish HNPCC families indicates that there may be geographic differences in the occurrence of HNPCC. However, this does not change the fact that identification of HNPCC—perhaps one of the most common inherited diseases identified in humans—has become a question of vital importance now when diagnosis of the syndrome and large-scale screening of gene carriers using specific tests are on the horizon. [Key words: Hereditary cancer; Hereditary colorectal cancer; Hereditary colon cancer, frequency]

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Hereditary nonpolyposis colorectal cancer (HNPCC) is an autosomal dominant cancer syndrome characterized by early onset of colorectal carcinomas (CRC), proximal tumor excess, high risk of metachronous disease, and excess of other cancers (especially endometrial, gastric, uroepithelial, and biliopancreatic tumors) in kindred.[1–3] HNPPC has also been referred to as the Lynch syndrome[4] or as cancer family syndrome.[5] Identification of HNPCC has great practical importance both in relation to adapting methods of treating affected gene carriers to the lifelong risk of metachronous malignancies and because asymptomatic high-risk family members are ideal subjects for cancer screening.

Estimates of the proportion of HNPCC of all CRC patients vary between 1 and 10 percent. Most appraisals indicate a proportion of 2 and 5 percent of all CRCs. However, there have been few studies in this field. Most of these are retrospective and based on series from one institution[6, 7] or on series selected by age.[8, 9] Two population-based studies—one retrospective and one prospective—have been published, both of which represent areas with about 0.25 million inhabitants.[10, 11] Genetic linkage to loci on chromosomes 2p and 3p was recently demonstrated in HNPCC families,[12, 13] and the respective genes, hMSH2 and hMLH1, were later cloned.[14–17]

The purpose of the present study was to design a

nonselected, prospective, multicenter study, taking into account family background and other risk factors of CRC. The situation in Finland is favorable to this kind of study. The population (5 million) is ethnically homogenous, and the country has been divided into hospital districts with a population-based responsibility for health care. Nationwide and complete registers for death certificates and cancer patients enable reliable verification of cancer cases. In the present study family history and other risk factors of all new CRC patients were studied during a 12-month period in six district hospitals and in four university hospitals located in different parts of the country. Patients comprised 23 percent of all CRCs diagnosed in Finland during the study period.

METHODS

Study Protocol

Over a 12-month period (September 1, 1990 to August 31, 1991) a local surgeon belonging to the study group interviewed all patients with new primary adenocarcinoma of the colon or rectum. A one-page questionnaire was filled in. Known risk conditions of CRC (ulcerative colitis, familial adenomatous polyposis, and previous malignancies) were evaluated for the proband. Occurrence of malignancies in first-degree and second-degree relatives was elicited by interviewing the patient. Questionnaire and copies of the hospital records were sent to the responsible investigator (J-P. M.), who analyzed the material and took charge of obtaining any further records and genealogic data required. Altogether, 406 new colorectal cancer patients were included in the study.

Classification of Family History

Families were divided into three categories according to cancer status among family members: 1) negative family history, 2) positive family history, and 3) patients with ulcerative colitis or familial adenomatous polyposis coli (FAP). 1) Negative family history group (375 probands; 92.4 percent) comprised families with no family members affected by cancer and families with one or two first-degree/second-degree family members with malignancies of any type, although age of patients and/or tumor spectrum was not indicative of any inherited cancer syndrome. Information contained in response to questionnaires was supplemented only occasionally.

2) Positive family history group (24 probands; 5.9 percent) included families with three or more first-degree relatives with a malignancy or families with features—such as early onset, multiple metachronous tumors, or a typical tumor spectrum—indicative of hereditary cancer syndrome in first-degree and/or second-degree relatives. In this group, family history and verification of cancer were completed by obtaining documents when available. In total, 126 family members with malignancy (mean, 5.3 per family) were identified by questionnaire in these 24 families. Only one-half of these cases could be verified by documents. However, in verified or suspected HNPCC families and in families with a middle-aged (under 50–60 years of age) proband, documents could be obtained in almost all cases. 3) The third group comprised seven (1.7 percent) probands with UC or FAP, all of whom had clinical and histologic documentation of their disease.

Criteria for HNPCC

A family meeting the Amsterdam criteria[5] was considered a HNPCC family. Families with a dominant cancer trait and features indicative of HNPCC but not meeting the Amsterdam criteria were considered suspected or putative HNPCC families.

Incidence of Colorectal Cancer in Finland

CRC is the third most common malignancy in Finland after carcinoma of the breast and lung. Finland is a low-incidence area for CRC, even though the total number of cases is strongly on the increase because of the aging population. In 1988, the age-specific incidence of CRC in Finland (males 18, females $15.5/10 \times 10^5$) was, for example, one-half that in Denmark (males 35.9, females $29.3/10 \times 10^5$).[18]

Registers Used

Parish Registers. A very exact and reliable population register has been kept in local parishes in Finland since the 1600s. In addition to general biographic data, these registers also file the cause of death for each parish member. This information, originally based on diagnoses by clergy, became more reliable after 1936 when a medical death certificate became mandatory throughout the country.

Register of the Cause of Death. Since 1936, all death certificates have been preserved in the Central Statistical Office of Finland and are available for research purposes. The death certificate also includes information about hospitalization and consulting physicians,

thus enabling hospital records to be obtained when they have been preserved or filed on microfiche.

Finnish Cancer Registry. The Finnish Cancer Registry was established in 1952. Since 1961 reporting of cancers has been compulsory, so that the registration of cancers in Finland is virtually complete.[19] The register, which is data-based, is accessed by means of an individual's social security number, which makes it possible to check whether that person has had a malignancy during the last 30 to 40 years.

Patients

Reliable data on status of first-degree relatives was obtained by interview for all 406 patients with new, primary CRC treated during the study period in the ten participating hospitals. According to statistics of the Finnish Cancer Register, the number of new CRCs in Finland in 1990 was 1,738. Thus, our probands represent 23 percent of all CRCs diagnosed in Finland during the study period.

Mean age of patients was 66.6 (range, 29–91) years. Age distribution is shown in Figure 1.

Regional Health Care in Finland

Finland has been divided into 22 health care districts, each with one central hospital that has responsibility for the population in that district. Some additional local hospitals share responsibility for health care in densely populated areas. Five of the central hospitals are university hospitals, with more extended responsibility in demanding and uncommon health care.

Six of the central hospitals with a mean population of 165,000 (range, 72,000–250,000) and four of the university hospitals situated in different parts of the country participated in the study. Patients (N = 200; 49 percent) in the six central hospitals represent a nonselected, population-based series, whereas patients (N = 206; 51 percent) in university hospitals are more or less selected.

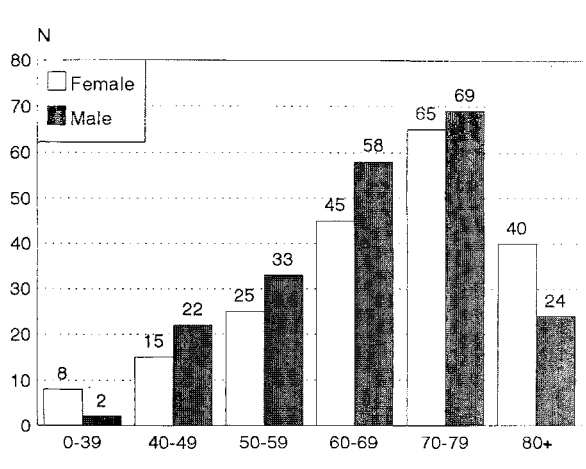

Figure 1. Age and sex distribution of 406 patients with colorectal cancer.

RESULTS

A negative family history was observed in 375 (92.4 percent) patients. However, two patients in this group had had multiple metachronous intestinal malignancies at a young age without polyposis. A male patient had colonic cancer at ages 28 and 44, and another male patient had colonic cancer at ages 43 and 63 and synchronous adenocarcinoma of the rectum and jejunum at age 67. The remaining 31 patients were divided as shown in Table 1. Fourteen (3.4 percent) had three or more first-degree relatives with a malignancy, but family history, tumor spectrum, and/or age distribution were not indicative of HNPCC.

In seven (1.7 percent) cases HNPCC could be suspected, but the families did not meet the Amsterdam criteria. In three of these, there was no person with CRC diagnosed who was under 50 years of age (so-called late onset family). In two families, a patient with an extracolonic malignancy (uterus, esophagus) prevented the Amsterdam criteria from being met. In one small family with two affected members, the proband had had three metachronous malignancies (colon, bilateral breast cancer) before age 50, and her father had died of CRC at the age of 35. In another family, the proband had had two CRCs at age 75 and breast cancer at age 72. Her only son had CRC at age 28. These seven families were considered to be putative HNPCC cases.

In three cases (0.7 percent) the Amsterdam criteria were fulfilled. Two of the families with 6 and 33 affected family members in two and four generations, respectively, were typical HNPCC families according

Table 1.
Distribution of Hereditary and Other Risk Conditions in 406 Patients with Colorectal Cancer

Risk Condition	No. of Patients (%)
Putative HNPCC	7 (1.7)
Verified HNPCC	3 (0.7)
Ulcerative colitis	4 (1.0)
Familial adenomatosis polyposis	3 (0.7)
Previous colorectal cancer	14 (3.4)

to age distribution and tumor spectrum. In the third family, only one of five patients had been under 50 years of age at the time cancer was diagnosed.

A colorectal carcinoma was complicating ulcerative colitis in four (1.0 percent) patients and familial adenomatous polyposis was found in three (0.7 percent) patients. A synchronous colorectal neoplasia was observed in 30 (7.4 percent) patients (adenoma(s) in 27, carcinoma in 3). A previous malignancy was diagnosed in 28 (6.9 percent) patients. The most common metachronous tumors were CRC (14 cases) and endometrial carcinoma (5 cases).

DISCUSSION

This prospective multicenter study gives an estimate of frequency of HNPCC in Finland, which is lower than our previous estimate based on a retrospective analysis in one hospital district. In retrospective analysis of all CRC patients (N = 468) treated within a ten-year period (1970–1979) in the province of Central Finland, proportion of verified HNPCC was 3.8 percent and 5.5 percent when putative HNPCC cases were also included.[10] In the present multicenter analysis, corresponding figures were 0.7 and 2.4 percent.

The present study is geographically more representative, and probands comprise 23 percent of all CRCs diagnosed in Finland during the 12-month period. The method used to investigate family history and obtain documents was identical in both studies. However, the study period (12 months) is short and may predispose to an underestimate caused by chance. In addition, it is probable that systematic screening for CRC initiated in 1983 in about 60 Finnish HNPCC families has prevented the formation of some CRC cases in HNPCC patients. Effectiveness of this screening has been analyzed in a series of 22 Finnish HNPCC families, and a remarkable reduction in occurrence of CRC could be demonstrated because of polypectomies in screened subjects.[20]

Another possible bias, which cannot be excluded in retrospective analysis, is the possibility of local overpresentation of HNPCC in the province of Central Finland (population, 0.25 million). In fact, a certain concentration of HNPCC cases in this previous study was observed simply because affected members of two large HNPCC families (Nos. 1 and 2) constituted 6 of 18 definitively diagnosed hereditary cases.[10] Subsequently, it has been possible to demonstrate the presence of a widespread, single ancestral founding mutation in central and eastern Finland.[21]

It is also worth noting that the Amsterdam criteria had not become available in 1987. Two of 13 families (15 and 18) did not meet the Amsterdam criteria because there were no affected family members under 50 years of age. According to present criteria these families would be classified as putative HNPCC families. Even if these two cases were excluded, the proportion of cases meeting the Amsterdam criterion was 3.4 percent of all CRCs.[10]

Ponz de Leon *et al.*[11] evaluated family history of 389 consecutive patients with CRC in the Modena district (population, 0.26 million) in Italy. The authors found that 15 (3.9 percent) probands had two or more relatives with CRC. Unfortunately, these families were not presented or classified in detail, and no age criterion was used. These families have subsequently been re-evaluated, with the final proportion of identified HNPCC cases representing 3.4 percent of all CRCs.[22]

Westlake *et al.*[8] found HNPCC in 3.1 percent of 318 patients with CRC under 50 years of age and listed on the Alberta Cancer Registry in Canada. Family history was studied using a questionnaire. However, the proportion of HNPCC was only 0.3 percent of all CRC cases listed on the cancer registry.

Kee and Collins[9] retrospectively investigated all patients with nonpolyposis CRC under age 55 years (N = 205) diagnosed within a three-year period in Northern Ireland. The vital status of all first-degree relatives was established. They found 13 probands with two or more relatives affected with CRC, *i.e.*, 6 percent of the study patients and 1 percent of all CRC patients. On the basis of their results, the authors estimated that the proportion of HNPCC might be between 1 and 2.6 percent.

Stephenson et al.[6] found four (4 percent) cases with verified or putative HNPCC when family history of 100 patients with apparently sporadic CRC was evaluated. Ages of the probands and affected family members were not presented.

Aaltonen *et al.*[23] used a novel approach to estimate the frequency of HNPCC. All CRC patients (N = 227) under 45 years of age diagnosed over a five-year period in Finland comprised the probands. Pedigrees of the probands were constructed by combining information from the Finnish Population Register Center and Finnish Cancer Register, using automatically processed data. On the basis of their results, the authors

suggested that the proportion of HNPCC of all CRCs would be between 0.5 and 0.9 percent.

The crucial weakness in all studies evaluating prevalence of HNPCC has been the fact that a specific phenotype or biomarker has not been available for identification. In an attempt to standardize publications in this field, the International Collaborative Group on HNPCC agreed in 1990 that the Amsterdam criteria should be used as the minimum criteria for inclusion of HNPCC families in publications.[5] However, the Amsterdam criteria are not definitive for HNPCC; rather they are useful tools, ensuring that families in publications and collaborative studies are comparable with each other. For practical reasons, it has been impossible, for example, to include all possible extracolonic malignancies belonging to the tumor spectrum of HNPCC in the criteria, even though they might be important in diagnosing the syndrome.

In the present study, the proportion of identifiable risk factors of CRC was 5.8 to 7.5 percent (HNPCC, 0.7–2.4 percent; previous CRC, 3.4 percent; ulcerative colitis, 1.0 percent; FAP, 0.7 percent). Proportions of both ulcerative colitis and FAP are overestimates because of centralization of these diseases in university hospitals participating in the study. The real proportion of cancer caused by ulcerative colitis might be one-half of the observed 1 percent and of cancer caused by FAP about 0.2 to 0.3 percent when more than one-half of new FAP cases are now identified by family screening and treated prophylactically.[24]

Our study demonstrates that it is difficult to give an indisputable answer to the question of prevalence of a cancer syndrome, which cannot be diagnosed until several family members have been affected. Based on the present study and previous analysis, it may be concluded that the proportion of classical HNPCC diagnosed by family history of all CRCs varies between 1 and 4 percent in different studies, depending on study protocol, selection of patients, and criteria used for hereditary cases.

Recently, a HNPCC gene was mapped to the short arm of chromosome 2 by linkage analysis in two large kindreds[12] and possibly also cloned.[14, 15] A second locus predisposing to HNPCC was found in chromosome 3 in two kindreds by Lindblom *et al.*,[13] and this has also recently been cloned.[16, 17] Synchronously, an analysis of fresh frozen tumor specimens of HNPCC patients provided evidence for a novel mechanism of carcinogenesis, a tendency to microsatellite instability at multiple random loci throughout the genome.[25] This abnormality referred to as the replication error phenomenon was found in approximately 15 percent of sporadic CRCs, and it may offer a screening assay for selection of patients with increased risk of hereditary cancer.[25–27]

Use of specific gene tests or replication error phenomenon would enable more exact estimates—for example, identification of so-called new mutations—in the future. However, what is still obscure is whether the occurrence of HNPCC is equal in all geographic areas. Recent studies have shown that there are remarkable differences in the occurrence of HNPCC, even in a small country such as Finland. Many apparently unrelated HNPCC families share a common ancestral founding mutation,[21] and cases with "new mutation" are not as common as expected, at least in Finland.

However, it is worth noting that even when accepting the lowest estimate (about 1 percent) for the proportion of HNPCC it would mean, for example, in the United States more than 1,500 new cases of HNPCC every year. Therefore, HNPCC, which is possibly one of the most commonly inherited diseases identified so far, has great practical importance in prevention of CRC in younger age groups.[20] Its significance will still increase as the use of specific gene tests will, within a short time, enable highly targeted prevention among persons with 100 percent risk of CRC.[28, 29]

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