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Incidence of hereditary non-polyposis colorectal cancer (HNPCC) in the city of Szczecin, north-western Poland

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Abstract. The study population consisted of 140 consecutive colorectal cancer patients, inhabitants of the city of Szczecin, north-west Poland, who were histopathologically diagnosed in the period of 2 years – 1991-1992. Family history was obtained in 124 (88.6%) of patients. A definitive diagnosis of HNPCC was established if requirements of the International Collaborative Group on HNPCC (ICG-HNPCC) were met. Suspected HNPCC were recognised according to criteria described by Ponz de Leon or Mecklin or Kunitomo. HNPCC as defined by International Collaborative Group on HNPCC was identified in 2 (1.6%) families. Suspected HNPCC were recognised in 16.9%, 3.2% and 4.0% of patients if Ponz de Leon or Mecklin or Kunitomo criteria were applied, respectively. In our series in 19 of 124 cases, colorectal carcinomas were diagnosed in patients under 50 years of age. Only in one of these cases, features characteristic of HNPCC other than young age were found which suggests that in our region the frequency of somatic or germ line de novo mutations in genes predisposing to colorectal cancer may be high. Our results suggest that the frequency of HNPCC inherited from ancestors in Poland and other countries is approximately similar and this syndrome is common disease everywhere.

Key words: HNPCC, incidence.

Introduction

A family with hereditary non-polyposis colorectal cancer (HNPCC) was first reported by WARTHIN in 1913 and later was characterised in more detail by LYNCH and KRUSH (1971).

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HNPCC is an autosomal dominant condition caused by the loss of function of a mismatch repair genes (FISHEL et al.1993, LEACH et al. 1993, NICOLAIDES et al. 1994, PAPADOPOULOS et al. 1994). It is characterised by the development of colorectal cancer (CRC) at an early age, a predilection for tumours in the proximal colon, an excess of multiple CRC, and an association with various extracolonic cancers including endometrial cancer (LYNCH et al. 1988, WATSON, LYNCH 1993). According to the International Collaborative Group on HNPCC (ICG-HNPCC) this syndrome can be diagnosed when:
1) at least three relatives should have histologically verified colorectal cancer; one of them should be a first degree relative to the other two. Familial adenomatous polyposis should be excluded, 2) at least two successive generations should be affected, 3) in one of the relatives colorectal cancer should be diagnosed under 50 years of age (VASEN et al. 1991).

Periodic examinations of high risk family members may prevent the development of disease and death from cancer. Surveillance programmes including DNA analyses, colonoscopy and other screening tests should be an important goal of health-care programmes (FITZGIBBONS et al. 1987, BENATTI et al. 1993, MECKLIN, JARVINEN 1993, LYNCH et al. 1994, VASEN 1994, VASEN et al. 1995). It seems reasonable to apply surveillance measures not only in families with definitive HNPCC but also in a group with so-called "suspected HNPCC" where Amsterdam criteria are not fully met, but HNPCC cannot be reasonably excluded. In order to evaluate the numbers of DNA tests and diagnostic clinical procedures necessary for realisation of HNPCC targeted screening programmes the analyses of the disease frequency are needed.

In the studies performed by various authors the minimum frequency of HNPCC ranged between 0.2-6% in different populations (MECKLIN 1987, PONZ de LEON et al. 1989, 1993, 1995, KEE, COLLINS 1991, WESTLAKE et al. 1991, STEPHENSON et al. 1991, KUNITOMO et al. 1992, MECKLIN et al. 1995). The incidence of definitive and suspected HNPCC in Poland has not been studied before.

Material and methods

The studied population consisted of all 140 consecutive patients, inhabitants of the city of Szczecin (~400 000 of inhabitants), with CRC diagnosed within the period of 2 years, 1991-1992, in any of all 5 histopathology departments working in the area. Patients were included if they had adenocarcinoma and excluded if they had other histologic types of cancers or conditions known to

predispose to colorectal carcinoma such as familial adenomatous polyposis or inflammatory bowel disease.

The medical records of the patients who fulfilled the entry criteria were used to obtain the address of the patient or the next of kin of diseased patients. A questionnaire was sent to the patient or next of kin inquiring about the family history of cancer in the patients family. Participants were asked to list first- and second-degree relatives with a history of cancer, whether the relative was from the paternal or maternal side of the family, and the type of cancer the relative had. Additionally, we asked for addresses and phone numbers of these relatives so that we could contact them to confirm the diagnosis and to inquire if they had further knowledge of the family cancer history. If the patient was diseased and the letter was sent to a surviving spouse, we also asked them for the name and address of a brother or sister of the patient we could contact. If the letter was not returned within one month, a telephone interview about the family history was attempted. Of the 140 patients with CRC a family history was obtained in 124 cases (88.6%). Other patients were lost to follow up or refused to participate. Whenever possible the diagnosis of cancer in relatives was verified not only by interviews but also by review of medical records and death certificates. Although direct verification (i.e. clinical charts or death certificates) was possible only in ~40% of the relatives, it revealed an almost complete agreement between the information derived from interviews and data

Table 1. Definition of "Suspected HNPCC"

A. Ponz de Leon et al. (Benatti et al. 1993; Ponz de Leon et al.1993, 1995).
1. Familial aggregation of neoplasms* and/or
2. Multiple primaries** and/or
3. Early development (before age 50) of colorectal cancer
B. Mecklin (1987)
Patients with colorectal carcinoma who had two or more first-degree relatives with other intraabdominal malignancy (e.g., uterus, stomach, pancreas)
C. Kuntomo et al. (1992)
Group A: A family with three or more colorectal cancer patients within the first degree relatives
Group B: A family with two or more colorectal cancer patients within the first degree relatives and with any of the followings: a) age of onset of colorectal cancer is younger than 50 years old; b) right colon involvement;c) synchronous or metachronous multiple colorectal cancers; d) association with extra colorectal cancers

* Familial aggregation – in the sibship of the proband, 50% (or more) of the siblings affected by cancer of all sites or in the whole family (parents, siblings, offspring) 50% (or more) of the family members affected by cancer of all sites.

** Multiple primaries – in the proband, or in a first-degree relative, presence of two (or more) independent primary cancers (either in the large bowel or in other organs)

from official certificates. A definitive diagnosis of HNPCC was established if requirements of the ICG-HNPCC were met (VASEN et al. 1991). Suspected cases of HNPCC were identified using criteria defined by PONZ de LEON – Table 1A (BENATTI et al. 1993, PONZ de LEON et al. 1993, 1995), MECKLIN (1987) – Table 1B, and KUNITOMO et al. (1992) – Table 1C.

Results

Of the 124 patients with CRC a definitive diagnosis of HNPCC (i.e. fulfilment of ICG-HNPCC criteria) was established in 2 (1.6%) cases. An example of kindred with definitive HNPCC is shown in Fig. 1.

Table 2A. Suspected HNPCC according to Ponz de Leon criteria (BENATTI et al. 1993, PONZ de LEON et al. 1995)

Case No.	Age of onset < 50 years	Familial aggregation	Multiple primaries
1	+	–	–
2	+	–	–
3	+	–	–
4	+	–	–
5	+	–	–
6	+	–	–
7	+	–	–
8	+	–	–
9	+	–	–
10	+	–	–
11	+	–	–
12	+	–	–
13	+	–	–
14	+	–	–
15	+	–	–
16	+	–	–
17	+	–	–
18	+	–	–
19	+	+	+
20	–	+	–
21	–	–	+

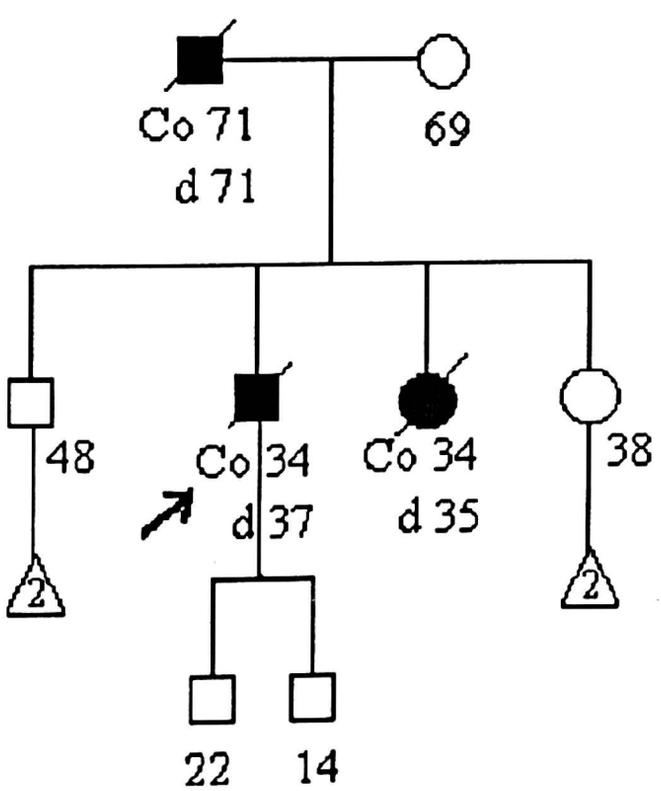
Table 2B. Suspected HNPCC according to Mecklin criteria (MECKLIN 1987)

Case No.	Aggregation of intraabdominal malignancies in family
8	+
20	+
22	+
23	+

Table 2C. Suspected HNPCC according to Kunitomo criteria * (KUNITOMO et al. 1992)

Case No.3	≥ 3 colorectal cancer within I° relatives	≥ 2 colorectal cancers within I° relatives with:			
		age of onset < 50 yrs	right colon involvement	synchro- or metachronous colorectal cancers	association with extra colorectal malignancy
16	–	+	–	–	–
19	–	+	+	–	+
23	–	–	–	–	+
24	–	–	+	–	–
25	–	–	–	–	+

* Cases with fulfilment of HNPCC criteria according to ICG-HNPCC not included.



Suspected HNPCC according to PONZ de LEON criteria was diagnosed in 21 (16,9%) cases – Table 2A. Most frequently (18 cases) the only feature indicating HNPCC was early age of onset (patients under 50).

Suspected HNPCC according to MECKLIN and KUNITOMO criteria was identified in 4/124 (3,2%), and 5/124 (4,0%) of cases, respectively – Tables 2B and 2C. In cases No. 8

Fig. 1. Definitive HNPCC with fulfillment of criteria according to ICG-HNPCC
Legend – see Fig. 2

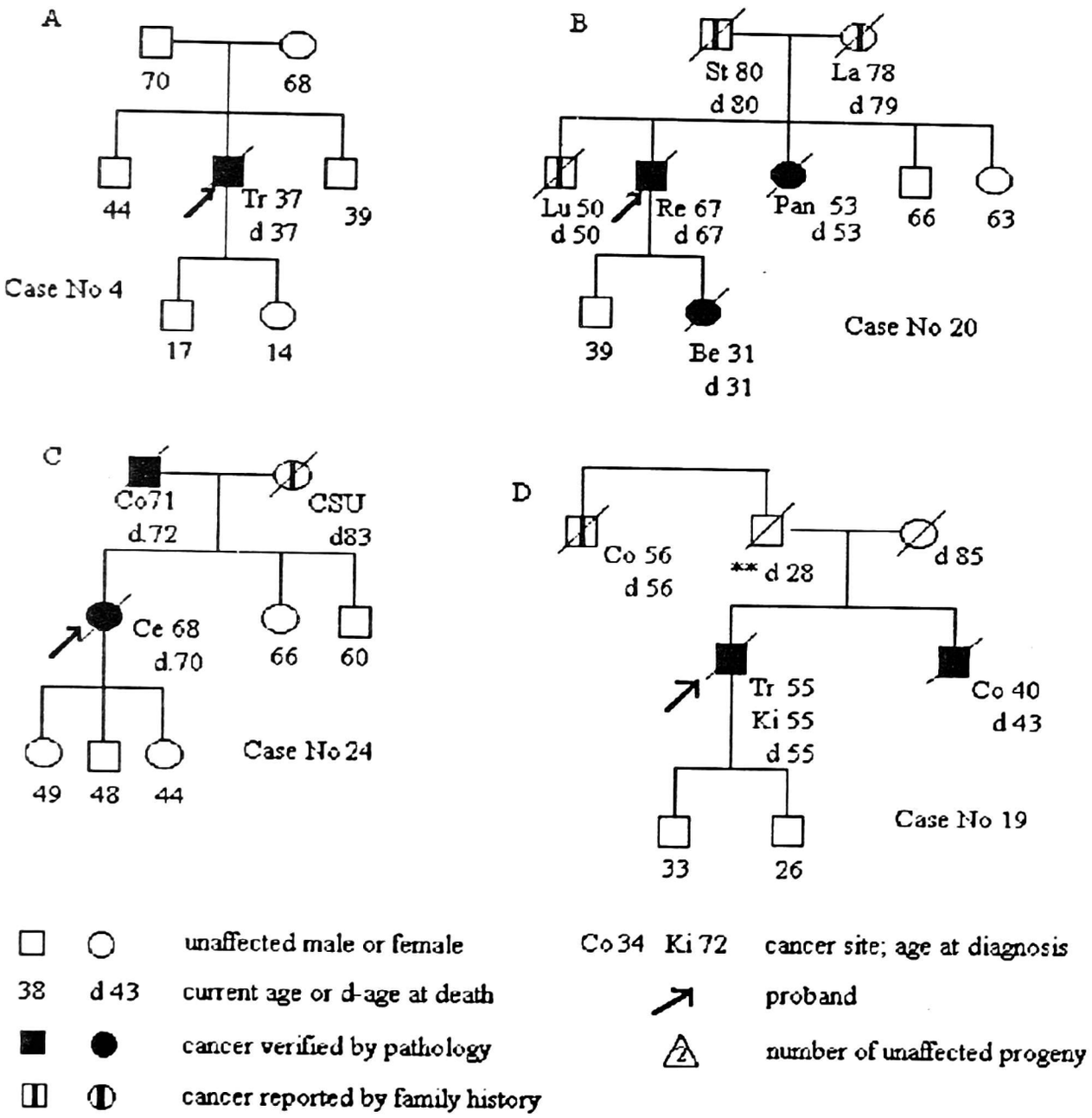


Fig. 2. Suspected HNPCC with fulfillment of criteria according to: A – Ponz de Leon, B –Mecklin and Ponz de Leon, C – Kunimoto, D – Ponz de Leon and Kunimoto
Cancer sites: Co – colon, Ce – cecum, Tr – transverse colon, Re – rectum, Lu – lung, Ki – kidney, CSU – cancer site unknown, St – stomach, La – Larynx, Pan – pancreas, Be – breast

and 20 not only PONZ de LEON but also MECKLIN criteria of suspected HNPCC were met. Suspected HNPCC could be recognised by either PONZ de LEON or KUNITOMO criteria in cases No. 16, 19. Case No. 23 was diagnosed as suspected HNPCC according to MECKLIN and KUNITOMO criteria. Examples of kindred with suspected HNPCC are shown in Fig 2.

Discussion

Although HNPCC has been described in many races and populations including Europeans, White and Indian Americans, Australians, Asians and South

Americans (SARROCA et al. 1978, BAMEZEI et al. 1984, LYNCH et al. 1985, 1991, USHIO 1985, SAN ROSE et al. 1989, VASEN et al. 1990, MECKLIN, JARVINEN 1991, JASS, STEWARD 1992), as far as we are aware, studies of this syndrome frequency have been carried out only in Finland, Italy, Northern Ireland, England, Canada and Japan (MECKLIN 1987, PONZ de LEON et al. 1989, 1993, 1995, KEE, COLLINS 1991, STEPHENSON et al. 1991, WESTLAKE et al. 1991, KUNITOMO et al. 1992, MECKLIN et al. 1995).

This study gives a rough estimate of HNPCC frequency in Poland. In a group of 124 consecutive cases of CRC diagnosed in 1991-1992 in inhabitants of the city of Szczecin, north-western Poland, HNPCC according to Amsterdam criteria was found in 1.6% of the patients (2 cases). Additionally suspected cases of HNPCC were recognised in 16.9%, 3.2% and 4.0% of patients if PONZ de LEON or MECKLIN or KUNITOMO criteria were applied, respectively (Table 3).

The number of cases analysed in this study is relatively low (~ 8000 new cases of CRC occur in Poland yearly), but probably bias in the assessment of HNPCC frequency in our population resulting from a small number of sample is not big – in analyses of 376 families willing to collaborate with us (but not consecutive cases) in Regional Hereditary Cancer Center we found similar prevalence of HNPCC cases (KŁADNY, LUBIŃSKI 1995).

Another drawback in our studies is low verification rate (~40%) of questionnaire data on cancer family history. However, as suggested by other authors

Table 3. Comparison of the freguency of colorectal cancer with features of definitive or suspected HNPCC between Szczecin (Poland) and other regions

Region	Definitive HNPCC	Suspected HNPCC	Total
A			
Modena (Italy)	4.1% (39/961)[a]	8.4 % (81/961)[b]	12.5% (120/961)
Szczecin (Poland)	1.6% (2/124)[a]	16.9% (21/124)[b]	18.5% (23/124)
B			
Central Finland	3.8% (18/472)[a]	1.7% (8/472)[c]	5.5% (26/472)
Finland Multicenter study	0.7% (3/406)[a]	1.7% (7/406)[d]	2.4% (10/406)
Szczecin (Poland)	1.6% (2/124)[a]	3.2% (4/124)	4.8% (6/124)
C			
Japan	0.2% (69/32470)[a]	2.2% (708/32470)[e]	2.4% (777/32470)
Szczecin (Poland)	1.6% (2/124)[a]	4.0% (5/124)[e]	5.6% (7/124)

[a] According to ICG-HNPCC (VASEN et al. 1991)
[b] According to Ponz de Leon (BENATTI et al. 1993; PONZ de LEON et al. 1995)
[c] According to Mecklin 1987 (MECKLIN 1987)
[d] According to Mecklin 1995 (MECKLIN et al. 1995)
[e] According to Kunitomo (KUNITOMO et al. 1992)

it is likely that since the study was limited to the first – and second degree relatives, bias due to inability to verify all cancer diagnosis should be minimal (SELLERS et al. 1987).

We studied only the city of Szczecin, but because of migration after the second war this population is probably representative for the entire country.

WESTLIKE et al. (1991) evaluated the frequency of HNPCC in Southern Alberta, Canada. Twelve families were identified as HNPCC, at a frequency of 3.1% of 390 cases. If "less strict" criteria were used for defining the syndrome, an additional 25 families could be included, thus raising the overall frequency to 9.5%.

KEE and COLLINS (1991) investigated all patients with nonpolyposis CRC before the age of 55 years (n – 205) diagnosed within a three-year period in Northern Ireland. The authors found that 13 individuals had two or more relatives affected by CRC which could be interpreted as HNPCC. These figures correspond to 6% of the studied group and to ~ 1% of all CRC registered in that period. Additionally 10 families with features suggestive of HNPCC were also found. KEE and COLLINS (1991) estimated that the prevalence of HNPCC in Northern Ireland might be about 1-2.6% of all CRC cases.

The main drawback of investigations performed by WESTLIKE et al. (1991) and KEE, COLLINS (1991) is that the analyses were limited to only a small fraction of registered patients. No family investigations were carried out in individuals older than 50 or 55 years who represent the large majority of CRC cases. In our studies a group of patients with CRC diagnosed under 50 or 55 years is small – 19 and 26 cases, respectively. We think that assessment of HNPCC frequency in such small group is not justified.

STEPHENSON et al. (1991) found four cases (4%) with definitive or suspected HNPCC among 100 patients with CRC from England. These results are again difficult to compare with ours because the age of the probants of affected family members was not given.

KUNITOMO et al. (1992) carried out a nation-wide survey for HNPCC in Japan in 1991. A total of 60 institutes all over country have joined the study. HNPCC as defined by Amsterdam criteria constituted 0.2% (69 patients) of 32470 CRC cases. Moreover, modified criteria of HNPCC (presented in Table 1C) were met in 2.2% of CRC. In our material, the frequency of definitive HNPCC and cases with fulfilment of Japanese modified criteria for HNPCC (but after exclusion of definitive HNPCC) was higher – 1.6% versus 0.2%, and 4.0% versus 2.2% (Table 3C) which suggests a higher incidence of HNPCC in our region.

In 1987 MECKLIN investigated familial cancer occurrence in a population study consisting of all CRC cases (n – 468) diagnosed in the province of Central Finland (0.25 million inhabitants) between 1970 and 1979. The observed findings provided HNPCC frequency about 3.8% of all registered CRC. In addition, there were eight patients (1.7%) who had two or more first-degree relatives with CRC or some other intraabdominal malignancy. These were considered as suspected HNPCC cases. In a subsequent multicenter study done in Finland (MECKLIN et al. 1995), the proportion of definitive HNPCC (Amsterdam criteria) was lower – 0.7% (3/406) of cases and 1.7% (7/406) of suspected HNPCC. Suspected HNPCC in the later report were diagnosed by criteria not clearly described and certainly different from those applied by MECKLIN in 1987, so it was impossible to compare the incidence of this group of cases in two reported studies from Finland. However, there is no question that the frequency of definitive HNPCC cases found in multicenter studies in Finland is much lower than that in Central Finland – 0.7% versus 3.8%. The suggested explanations for these differences are as follows: 1) a local overrepresentation of HNPCC cases in Central Finland and 2) a probable decrease in the proportion of familial cases of cancer owing to a systematic screening of CRC organised in Finland in the recent years.

In Szczecin we found a lower incidence of definitive HNPCC than in Central Finland – Table 3B (1.6% versus 3.8 %), but a higher prevalence of such cases than it was reported in multicenter studies in Finland (1.6% versus 0.7%). Suspected HNPCC using criteria applied by MECKLIN in 1987 were more frequent in Szczecin than in Central Finland (3.2% versus 1.7%).

PONZ de LEON et al. (1989, 1993, 1995) investigated familial occurrence of cancer in patients with CRC registered in Health District of Modena in Northern Italy. Accurate pedigrees limited to first – degree relatives, were traced in 893 out of 961 patients registered for CRC during 1984-1990. The families were then subdivided according to the presence, in the nuclear pedigree of six criteria (i.e. vertical transmission, familial aggregation, early age of onset, localisation in the right colon, multiple tumours and mucinous carcinoma), all indicative of an increased susceptibility to HNPCC. An genealogical trees showing 3 or more criteria and about 60% of pedigrees with 2 criteria were then extended to get information on second- and third-degree relatives. These detailed analyses allowed a reasonable projection of HNPCC frequency in the general population. The estimated frequency of definitive HNPCC was 4.1% and that of suspected HNPCC – 8.4% of all CRC. We found a lower incidence of definitive HNPCC – Table 3A (1.6% versus 4.1%), but a higher prevalence of suspected HNPCC (16.9% versus 8.4%). The extremely

high percentage of our CRC cases which according to Ponz de Leon criteria can be recognised as "suspected" HNPCC results mainly from one factor – a large number (19 of 21 cases) of CRC diagnosed in Szczecin under 50 years of age – Table 2A. Only in one of these cases (case No. 19) familial aggregation and multiple primaries could be simultaneously recognised. It raises a question whether the occurrence of CRC at young age in patients without other clinical features characteristic of HNPCC is a good criterion in the diagnosis of suspected HNPCC in our population. Generally in Poland ~ 20% of all CRC cases is diagnosed under 50 years of age. It is possible that in our country we have a higher number of somatic de novo mutations in genes predisposing to CRC. The frequency of HNPCC inherited from ancestors in Poland is at the level of a few percent of all CRCs, which is approximately similar to values previously reported for different populations. A real incidence of HNPCC in populations is certainly higher which is suggested by the occurrence of a large numbers of suspected cases. The actual HNPCC frequency can be more accurately assessed if population studies are based not only on pedigree analyses but if DNA tests are also be extended. Differences in the incidence of HNPCC across different ethnic groups cannot be excluded, but HNPCC in all populations seems to be common genetic disease.

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REFERENCES

BAMEZEI R., SINGH G.J., KARMA N.N., SIGH S. (1984). Genetics of site specific colon cancer. A family study. Clin. Genet. 26: 129-132.

BENATTI P., SASSATELLI R., RONCUCCI L., PEDRONI M., FANTE R., Di GREGORIO C., LOSI L., GELMINI R., PONZ de LEON M. (1993). Tumour spectrum in Hereditary Non-Polyposis Colorectal Cancer (HNPCC) and in families with "suspected HNPCC". A population-based study in northern Italy. Int. J. Cancer 54: 371-377.

FISHEL R., LESCOE M.K., RAO M.R.S., COPELAND N.G., JENKINS N.A., GARBER J., KANE M., KOLODNER R. (1993). The human mutator gene homolog MSH2 and its association with hereditary nonpolyposis colon cancer. Cell 75: 1027-1038.

FITZGIBBONS R.J., LYNCH H.T., STANISLAV G.V., WATSON P., LANSPA St., MARCUS J., SMYRK T., KRIEGLER M., LYNCH J. (1987). Recognition and treatment of patients with Hereditary Nonpolyposis Colon Cancer (Lynch Syndromes I and II). Ann. Surg. 206: 289-94.

JASS J.R., STEWARD S.M. (1992). Evolution of hereditary nonpolyposis colorectal cancer. Gut 33: 783-786.

KEE F., COLLINS B.J. (1991). How prevalent is cancer family syndrome ? Gut 32: 509-512.

KŁADNY J., LUBIŃSKI J. (1995). Incidence of hereditary nonpolyposis colorectal cancer in north-west Poland. Med. Genetik 2: 178.

KUNITOMO K., TERASHIMA Y., SASAKI K., KOMI N., YOSHIKAWA R., UTSUNOMIYA J., YASUTOMI M. (1992). HNPCC in Japan. Anticancer Research 12: 1856-1857.

LEACH F.S., NICOLAIDES N.C., PAPADOPOULOS N., LIU B., JEN J., PARSONS R., PELTOMAKI P., SISTONEN P., AALTONEN L.A., NYSTROM-LAHTI M., GUAN X.Y., ZHANG J., MELTZER P.S., YU J-W., KAO F-T., CHEN D.J., CEROSALETTI K.M., FOURNIER R.E.K., TODD S., LEWIS T., LEACH R.J., NAYLOR S.L., WEISSENBACH J., MECKLIN J.P., JARVINEN H., PETERSON G.M., HAMILTON S.R., GREEN J., JASS J., WATSON P., LYNCH H.T., TRENT J.M., De la CHAPELLE A., KINZLER K.W., VOGELSTEIN B. (1993). Mutations of a mutS homolog in hereditary nonpolyposis colorectal cancer. Cell 75: 1215-1225.

LYNCH H.T., DROUHARD T.J., SCHUELKE G.S., BISCONE K.A., LYNCH J.F., DANES B.S. (1985). Hereditary nonpolyposis colorectal cancer in a Navajo Indian family. Cancer Genet. Cytogenet. 15: 209-213.

LYNCH H.T., KRUSH A.J. (1971). Cancer family "G" revisited: 1895 - 1970. Cancer 27: 1505-1511.

LYNCH H.T., LANSPA S.J., BOMAN B.M., SMYRK T., WATSON P., LYNCH J.F., LYNCH P.M., CRISTOFARO G., BUFO P., TAURO A.V., MINGAZZINI P., Di GIULIO E. (1988). Hereditary Nonpolyposis Colorectal Cancer – Lynch Syndromes I and II. Gastroent. Clin. North. Am. 17: 679-712.

LYNCH H.T., SMYRK T.C., CAVALIERI J., LYNCH J.F. (1994). Identification of an HNPCC family. Am. J. Gastroent. 89: 605-609.

LYNCH H.T., SMYRK T., WATSON P., LANSPA St., BOMAN B., LYNCH P., LYNCH J., CAVALIERI J. (1991). Hereditary colorectal cancer. Seminars in Oncology. 18(4): 337-366.

MECKLIN J.P. (1987). Frequency of hereditary colorectal carcinoma. Gastroenterology 93: 1021-1025.

MECKLIN J.P., JARVINEN H.J. (1991). Tumor spectrum in cancer family syndrome (hereditary nonpolyposis colorectal cancer). Cancer 68: 1109-1112.

MECKLIN J.P., JARVINEN H. (1993). Treatment and follow-up strategies in hereditary nonpolyposis colorectal carcinoma. Dis. Colon Rectum 36: 927-929.

MECKLIN J.P., JARVINEN H.J., HAKKILUOTO A., HALLIKAS H., HILTUNEN K.M., HARKONEN N., KELLOKUMPU I., LAITINEN S., OVASKA J., TULIKOURA J., VALKAMO E. (1995). Frequency of Hereditary Nonpolyposis Colorectal Cancer – a prospective multicenter study in Finland. Dis. Colon Rectum 38: 588-593.

NICOLAIDES N.C., PAPADOPOULOS N., LIU B., WEI Y-F., CARTER K.C., RUBEN S.M., ROSEN C.A., HASELTINE W.A., FLEISCHMANN R.D., FRASER C.M., ADAMS M.D., VENTER J.C., DUNLOP M.G., HAMILTON S.R., PETERSEN G.M., De la CHAPELLE A., VOGELSTEIN B., KINZLER K.W. (1994). Mutations of two PMS homologues in hereditary nonpolyposis colon cancer. Nature 371: 75-80.

PAPADOPOULOS N., NICOLAIDES N.C., WEI Y-F., RUBEN S.M., CARTER K.C., ROSEN C.A., HASELTINE W.A., FLEISCHMANN R.D., FRASER C.M., ADAMS M.D., VENTER J.C., HAMILTON S.R., PETERSEN G.M., WATSON P., LYNCH H.T., PELTOMAKI P., MECKLIN J.P., De la CHAPELLE A., KINZLER K.W., VOGELSTEIN B. (1994). Mutation of a mutL homolog in hereditary colon cancer. Science 263: 1625-1629.

PONZ de LEON M., BENATTI P., PEDRONI M., SASSATELLI R., RONCUCCI L. (1993). Risk of cancer revealed by follow-up of families with Hereditary Non- Polyposis Colorectal Cancer: a population-based study. Int. J. Cancer 55: 202-207.

PONZ de LEON M., FANTE R., Di CANDIDO L., Di GREGORIO C., AMUSO D., BENATTI F., RONCUCCI L., LOSI L., De PETRI S. (1995). Epidemiology of tumors of the colon and rectum. Incidence, mortality, survival and familiality in the Health Care District of Modena, 1984-1992. University of Modena: 42-49.

PONZ de LEON M., SASSATELLI R., SACCHETTI C., ZANGHIERI G., SCALMATI A., RONCUCCI L. (1989). Familial aggregation of tumours in the three-year experience of a population-based Colorectal Cancer Registry. Cancer Research 49: 4344-4348.

SAN ROSE B.A., NAVARRO N.S., DOUBLE F. (1989). Hereditary nonpolyposis colorectal cancer; an awareness. JMMS 25: 37-38.

SARROCA C., GUADRELLI R., PRADERI R. (1978). Cancer coligue familial. Nouv. Presse Med. 7: 1412.

SELLERS T.A., OOI W.L., ELSTON R.C., CHEN V.W., WILSON J.E.B., ROTHSCHILD H. (1987). Increased familial risk for non-lung cancer among relatives of lung cancer patients. Am. J. Epidemiol. 127: 237-246.

STEPHENSON B.M., FINAN P.J., GASCOYNE J., GARBETT F., MURDAY V.A., BISHOP D.T. (1991). Frequency of familial colorectal cancer. Br. J. Surg. 78: 1162-1166.

USHIO K. (1985). Genetic and familial factors in colorectal cancer. J. Clin. Oncol. 15(suppl.1): 281-298.

VASEN H.F.A. (1994). Inherited forms of colorectal, breast, and ovarian cancer. Surgical Oncology Clin. N-Am. 3(3): 501-521.

VASEN H.F.A., MECKLIN J-P., MEERA KHAN P., LYNCH H.T. (1991). The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). Dis. Colon. Rectum 34: 424-425.

VASEN H.F.A., NANENGAST F.M., MEERA KHAN P. (1995). Interval cancers in hereditary non-polyposis colorectal cancer (Lynch syndrome). Lancet 345: 1183-1184.

VASEN H.F., OFFERHAUS G.J., den HARTOG JAGER F.C., MENKO F..H, NANENGAST F.M., GRIFFIOEN G., van HOGENZAND R.B., HEINTZ A.P.M. (1990). The tumour spectrum in hereditary nonpolyposis colorectal cancer: A study of 24 kindred's in the Netherlands. Int J.Cancer 46: 31-34.

WARTHIN A.S. (1913). Heredity with reference to carcinoma. Arch. Intern. Med. 12: 546-555.

WATSON P., LYNCH H.T. (1993). Extracolonic Cancer in hereditary nonpolyposis colorectal cancer. Cancer 71: 677-685.

WESTLAKE P.J., BRYANT H.E., HUCHCROFT S.A., SUTHERLAND L.R. (1991). Frequency of hereditary nonpolyposis colorectal cancer in Southern Alberta. Dig. Dis. & Sci. 36: 1441-1447.