Hereditary Tumors — Prophylactics, Early Diagnosis, Treatment

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It has been recently recognized that 5-10% of malignant tumors occurs as a result of high inherited predisposition which means that they are monogenic autosomal dominant diseases (1-3). The lifetime risk of cancer development in carriers of mutated genes predisposing for tumors approaches 90%. For years, it has been known that this mode of inheritance occurs only in some rare malignancies or syndromes predisposing for tumors such as retinoblastoma, familial polyposis coli or neurofibromatosis. Now, it is widely accepted, that monogenic dominant inheritance is a cause of a significant percentage of the so called 'common tumors' such as breast, colon or ovarian cancers.

Diagnosis of hereditary predispositions should include three major steps:
— pedigree analysis,

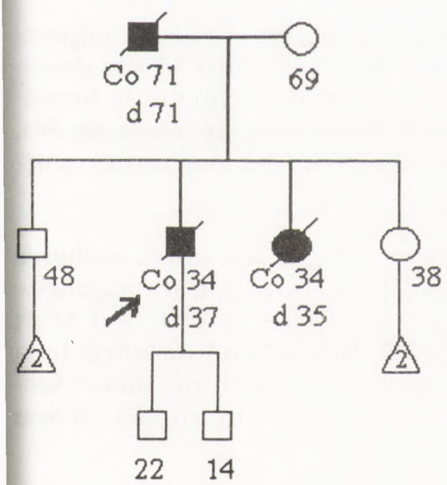

Fig. 1. A family with three relatives with colorectal cancer; two of them are first degree relatives in two generations; two tumors occur under age of 50. On the basis of these data definitive diagnosis of hereditary non-polyposis colorectal cancer (HNPCC) can be established.

— clinical examination,
— DNA tests.

Sometimes, hereditary tumors can be diagnosed just on the basis of pedigree analysis (see Fig. 1). However, in the majority of cases the examination of pedigrees provides only a "suspicion" of hereditary tumors (4).

The power of hereditary tumor diagnosis approaches could be significantly increased if pedigree analyses are performed in conjunction with clinical examination. There are more than 200 genetic syndromes predisposing for tumors which can be diagnosed by direct examination of patients by physicians (for example Peutz-Jegher, Ruwalcaba or Cowden syndromes) (2). Using pedigree analysis in conjunction with clinical data, it is possible to perform in many cases even such complicated differential diagnosis like differentiation between a few syndromes in which hereditary breast cancer can occur (Tab. 1).

TABLE 1

GENETIC DISORDERS ASSOCIATED WITH BREAST CANCER SUSCEPTIBILITY WHICH CAN BE DIAGNOSED BY PEDIGREE ANALYSIS IN CONJUNCTION WITH CLINICAL EXAMINATION

1. Site-specific hereditary breast cancer
2. Breast-ovarian cancer syndrome
3. Li-Fraumeni syndrome
4. Lynch II syndrome
5. Cowden disease
6. Peutz-Jegher syndrome
7. Rauwalcaba-Myre-Smith syndrome
8. Ataxia telangiectasia
9. Klinefelter syndrome

At present, pedigree analyses and clinical examination are really important, but certainly their role is going to be less significant due to the development of DNA tests. Examples of genes which, if mutated, can cause hereditary tumors development are listed in Table 2. In our center we study Rb, p53, VHL, MSH 2, MLH 1, BRCA 1 and BRCA 2 genes for diagnositic purposes.

What can we get by DNA tests?

1) Definitive diagnosis of hereditary tumors in the cases where pedigree analysis and clinical examination are not conclusive but indicate a genetic syndrome. In Figures 2 and 3 the first Polish mutations of VHL and MSH 2 genes respectively are presented. VHL gene mutation was detected in a patient with cerebellar hemangioblastoma from a family with no tumor history, but DNA test allowed for definitive diagnosis of von Hippel-Lindau syndrome.

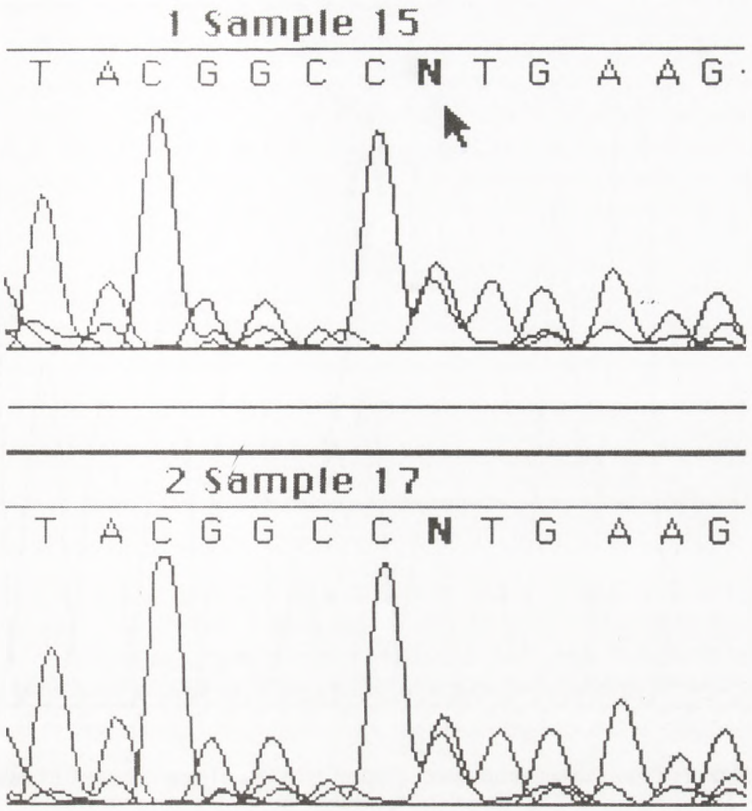

Fig. 2. Sequencing of VHL gene in two siblings of a family with suspicion of von Hippel-Lindau disease. Both are carriers of a heterozygous mutation C/T (marked as N on the charts below) in exon 1 of VHL gene (nucleotide 287) which causes a substitution of prolin to leucin in a corresponding aminoacid sequence.

TABLE 2
GENES ASSOCIATED WITH INHERITED PREDISPOSITION FOR TUMORS

Rb — retinoblastoma
p53 — Li-Fraumeni syndrome
Ret — MEN 2A
NF 1, NF 2 — neurofibromatosis
APC — familial adenomatous polyposis
MSH 2, MLH 1, PMS 1, PMS 2 } HNPCC
BRCA 1, BRCA 2 — brast cancer, ovarian cancer
ATM — ataxia telangiectasia, breast cancer?

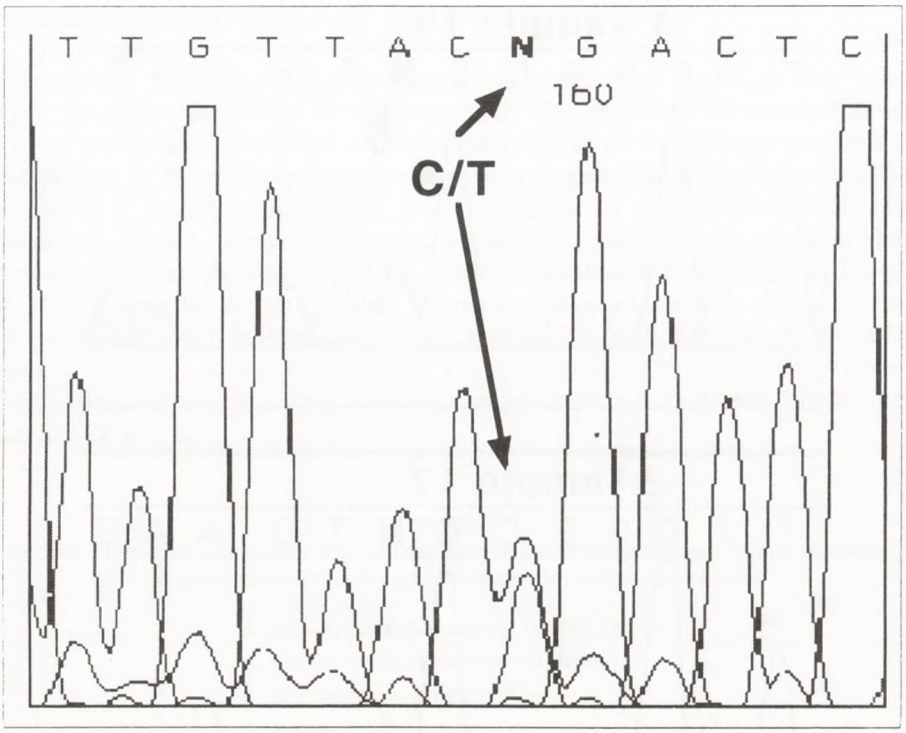

Fig. 3. MSH2 mutation in a family suspected of HNPCC. Heterozygous C/T substitution in exon 7 of the gene creates a stop codon (TGA) which causes protein truncation.

MSH 2 gene mutation was detected in a patient with colorectal cancer from family only "suspected" of hereditary predispositions. This allowed for definitive diagnosis of HNPCC (5).

2) Exclusion or confirmation of mutated gene carrier status in individuals from the families with hereditary predisposition for tumors (4,6,7). In Figure 4; pedigree of a family with constitutional MSH 2 gene mutation is presented. Only some individuals are carriers of the mutation (5).

Diagnosis of hereditary tumors is important because individuals from cancer-prone families need specific, other than routine, prophylactic, diagnostic and therapeutic measures (8-16).

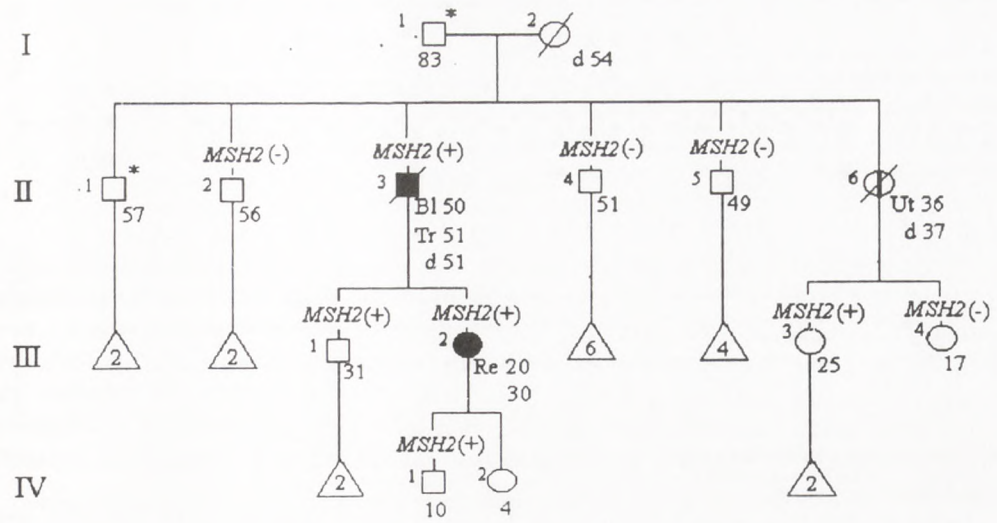

Fig. 4. Pedigree of a family suspected for HNPCC in which mutation carrier of MSH2 gene was discovered.

TABLE 3
PROPHYLACTICS OF HEREDITARY TUMORS — PHARMACOLOGY

Present	Future
Colon — Aspirin	— Gene transfer
Sulindac?	— Antisense
Piroxicam	— Other inhibitors of neoplastic transformation
Breast — Tamoxifen	
Regulation of?	
hormonal abnormalities	

TABLE 4
PROPHYLACTICS AND EARLY DETECTION OF TUMORS IN BREAST — OVARIAN CANCER SYNDROME

	Interval	Age
mammography (bleomycin test /-/)	1 yr	25-35 yrs
clinical examination + USG of breasts	6 mo	25 yrs
USG of genital tract (intravaginal) + CA 125 in serum	6-10 mo	25-35 yrs
prophylactic oophorectomy in a patient with breast cancer		
prophylactic oophorectomy in a woman after completion of her family plans		
prophylactic mastectomy?		
contrindication for hormonal treatment		

TABLE 5
SCREENING FOR EARLY DETECTION OF TUMORS IN HNPCC

	Interval	Age
colonoscopy and barium enema	2 yrs	20-25 yrs
USG of genital tract	2 yrs	25-30 yrs

Prophylactic management can include chemoprevention (for example selenium in the case of hereditary predisposition for stomach cancer, probably tomoxifen for carriers of mutated hereditary breast carcinoma genes — see Tab. 3), surgical resection (for example oophorectomy or sub-total colectomy in appropriately selected patients with high predisposition for ovarian or colon hereditary cancers) and careful selection of environment at workplace (e.g. prohibition of working at gas stations for individuals sensitive to benzen mutagenic effects).

Survaillance measures which lead to an early diagnosis of cancers are generally performed more frequently at a specific age and are focused on the examination of those organs which are particularly prone to malignant transformation (e.g. in families with HNPCC survaillance measures should include colonoscopies performed every 2 years beginning at the age of 25 and in women additional examination of uterus and ovaries — see Tables 4 and 5).

Surgical treatment of hereditary tumors is generally more radical (e.g. in HNPCC sub-total colectomy instead of regional resection is recommended), but in some instances more conservative (e.g. small renal cell carcinomas occuring in patients with von Hippel-Lindau disease should be monitored only and not resected until they obtain the size of 5 cm).

In our center we analyze ~ 6000 pedigrees and we perform ~ 700 clinical examinations every year. Our register includes ~ 300 families with high hereditary predisposition for tumors. A few dozen of early detected and property treated hereditary tumors of colon, breast, ovary and kidney have been reported.

The problem is really serious. Every year, ~ 5000 usually young individuals die in Poland due to hereditary tumors. In the majority of cases those patients do not have to die young. Many of them can even be completely cured if specific survaillance measures are applied.

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Summary

The authors describe the major rules of prophylactics, survaillance and treatment in patients with high hereditary predisposition for tumors on the basis of the experience of the first Polish hereditary cancer center, which was established in Szczecin in 1992.

Key words:
hereditary tumors, prophylactics, early diagnosis, treatment.

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