Tumors with familial occurrence

General information

Most human cancers occur **sporadically**. Their frequency in the family corresponds to the so-called **population risk**.

In the case of malignant transformation, it is caused only by **somatic** mutations, benign tumors represent a lower risk and tend to be surgically removed. Both **Proto-oncogenes** and **tumor suppressor genes** or **mutator genes** can be mutated in tumor tissue.

If a mutated tumor suppressor gene or a mutator gene is **transferred by the germ cell** of one of the parents and the mutation of the other allele occurs in the somatic cell, then we speak of a familial occurrence. Predisposition to a certain type of cancer is usually inherited. Approximately 10-15% of tumors are inherited; then the frequency of occurrence of a certain type of tumor in the family or pedigree is higher than its incidence in the population.

Typically, these are mainly mutations in tumor suppressor genes. These **mutations have a recessive character,** so to completely eliminate the tumor suppressor gene, it is necessary to exclude (mutations) both alleles of this gene (Knudson's theory of two interventions). However, from the point of view of clinical genetics, these **hereditary tumor syndromes are inherited autosomal dominantly (albeit with incomplete penetration).** This is due to the fact that a congenital (germline) mutation of the relevant tumor suppressor gene is a significant risk for the development of the relevant disease, which thus develops in the vast majority of people with the relevant germline mutation[1]

The familial occurrence of tumors is characterized by:

- **affecting several family members** with the same type of tumor;;
- **earlier onset of the disease** compared to the same type of tumor occurring sporadically;
- **multifocal** or **bilateral** occurrence;
- the emergence of one, two, sometimes even several primary tumors of different organs in the same individual (generally - **tumor multiplicity**).

Hereditary and sporadic tumors

Sporadic tumors

- most human cancers are random in the population - **sporadic** - meaning that gene mutations have only occurred in **somatic cells**
- **the frequency of cance**r in the family then corresponds to the population risk
- approximately every third **citizen** in our country will develop some form of cancer - most often **colorectal cancers** and **prostate tumors** in men, **breast cancers** in women
- protooncogenes, tumor suppressor genes and mutator genes **can be mutated** in tumor **combinations in various combinations**
- Mutations in **specific genes** - marker genes - are known for some types of tumors

The same type of cancer that occurs sporadically can have hereditary and familial occurrences (eg some tumors of the lung, breast, colon, melanoma, etc.).

Familial occurrence of tumors

- **a higher incidence of tumors** of a similar type in **more family members** is defined as a **familial incidence of cancer** when the genetic **cause (mutation) is unknown**
- in the **familial occurrence** of a certain type of tumor, the cause of the **same type** of tumor may be due to the **same environmental factors** as dietary habits (colon), high incidence of certain **viral diseases** (liver tumors - hepatitis B virus, etc.)

Hereditary tumor incidence

- if the mutated gene **is transferred by the germ cell** of one of the parents (germline mutation) and the mutation of the other allele occurs in the somatic cell , we speak of a **hereditary occurrence** of the tumor
- germline mutation transfer in most cases involves tumor suppressor genes or mutator genes
- **germline mutations** of two proto-oncogenes are currently known
- **inheriting a germline mutation** predisposes to a particular cancer
- an inherited character exists in approximately **5-10% of cancers**
- in this case, **the frequency of occurrence** of a certain type of tumor in the family is higher than its incidence in the population
- from the point of view of **formal genetics**, the occurrence of hereditary predisposed tumors appears as heredity typically **autosomal dominant with incomplete penetration**

- hereditary occurrence is characterized by involvement of **several family members with the same type of tumor** or a certain group of cancers (eg Lynch syndrome) and **earlier onset of the disease** compared to the same type of tumor occurring sporadically
- the incidence of the tumor is mostly **multifocal** or **bilateral** (bilateral acoustic neurinoma, multifocal and bilateral retinoblastoma, bilateral breast tumor)
- in some cases, one, two, and sometimes several **primary tumors** of different organs develop in the same individual
- in these families, the occurrence of one type of cancer **may indicate a risk of cancer** in another organ

- osteosarcomas, fibrosarcomas, melanomas occur in patients with **hereditary retinoblastoma**

- Ovarian tumors or small cell lung tumors also occur in predisposed individuals in patients with **hereditary breast cancer**

Selected cancer diseases with a familial occurrence

Neurofibromatosis

There are neurofibromatoses I and II. type. The disease affects the PNS, tumors - neurofibromas - are benign, but some patients have an increased incidence of malignant tumors of other organ systems. An example is an acoustic neurinoma (typical of type II neurofibromatosis). Their formation is conditioned by mutations in the chromosomal region: 17q11 (NF1 gene) and 22q12 (NF2 gene).

Li-Fraumeni syndrome

It is characterized by the occurrence of various types of hereditary primary tumors. Their formation is conditioned by a mutation in the tumor suppressor gene ***TP53*** (17p13.1).

Hereditary breast and ovarian cancer

It is caused by a mutation in the tumor suppressor gene ***BRCA1*** (17q21) or ***BRCA2*** (13q12). The cancer may be related to mutations in other genes (eg TP53 , PALB2 , CHEK2 , RAD51 , PTEN , STK11 , etc.).

- Breast cancer is **the most common malignancy** in women
- both sporadic and hereditary forms are formed by a **multi-step process** that involves activation of oncogenes and inactivation of tumor suppressor genes
- **aneuploidy** and **amplification** of some genes (HER2 / neu) is observed during karyological examination
- **inactivation of tumor suppressor genes** is often caused by point mutations in the gene on paired chromosomes or deletions of the gene / part of the gene
- in **hereditary types** of breast or breast and ovarian tumors, 2 tumor suppressor genes are used for diagnosis - **BRCA1 and BRCA2** (breast cancer ½)
  - **BRCA 1 gene mutation** is the cause of 52% of hereditary diseases
  - **BRCA 2 gene mutation** is the cause of 32%
  - 16% of patients with hereditary breast cancer have an inherited syndrome caused by **mutations in other genes**

- the products of both BRCA genes are involved in the maturation of the mammary gland and form complexes with the products of other genes , thus participating in the course of the cell cycle and in the repair of **double-stranded DNA breaks**
- **BRCA1 inherited mutation** occurs in women in families with familial breast, ovarian or breast and ovarian cancer

Familial adenomatous polyposis

It is caused by a mutation in the tumor suppressor gene ***APC*** (5q21-22), a rarer variant is caused by a mutation in the mutator gene ***MUTYH*** (1p32-34).

- Colorectal polyposis with the development of colorectal cancer.

Hereditary nonpolyposis colorectal cancer - Lynch Syndrome I and II

It is caused by mutations in various mutator genes (eg. *MSH2*, *MLH1*, *PMS1*, *PMS2*).

- Colorectal cancer without previous polyposis (HNPCC).

Peutz–Jeghers syndrome

Caused by a mutation in the *STK11* gene.

- Colon polyposis associated with typical pigmentations (not only) in the oral cavity.

Wilms' tumor

Caused by a mutation in the ***WT1*** (11q13) gene.

Familial retinoblastoma

Caused by a mutation in the tumor suppressor gene ***RB1*** (13q14).

Familial malignant melanoma

Caused by a mutation in the tumor suppressor gene ***MLM*** (9q21).

Further examples of disease familial occurrence

- Stomach tumor;
- Bladder Cancer;
- Cervical cancer;
- Lung tumor.

References

Related Articles

- Proto-oncogenes
- Tumor suppressor genesmutator genes
- Mutator genes, genome stability
- Incidence of Tumors

- Neurofibromatosis
- Wilms' tumor

- Ataxia telangiectasia
- Bloom syndrome
- Fanconi anemia

References

1. Hereditární nádorové syndromy | Genetika - Biologie. Genetika - Biologie | Váš zdroj informací o genetice a biologii [online]. Copyright ©2010 [cit. 07.12.2018]. Dostupné z: http://www.genetika-biologie.cz/hereditarni-nadorove-syndromy

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