Principles of genetic predisposition to malignancies

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It is estimated that around 30% of all malignancies are caused by a "high-risk" genetic predisposition [1]. This estimation is based on an evaluation of occurrence of disease among monozygotic twins. If one of them is affected with prostate (PC) or breast cancer (BC), then the probability of occurrence of this disease in the second sibling is 40% for PC and 30% for BC [2]. The concordance among monozygotic twins is even higher when occurrence of malignancies regardless of the site of origin is taken into consideration (e.g. breast cancer in one individual, stomach cancer in the sibling).

Genetic susceptibility to cancer can be divided into monogenic and polygenic predisposition.

Monogenic predisposition to cancer

Such diseases are caused by constitutional mutations of single genes, present in all cells of the body. DNA mutations can be detected in all malignancies. In the majority of cases somatic mutations are identified – changes which are present in malignant tissue only. To date, among hereditary causes of malignancies, the most frequently diagnosed background detected in routine molecular testing of the patients is monogenic predisposition with autosomal dominant type of inheritance. Each individual has two copies (alleles) of the gene responsible for a particular feature or disease, in the same locus on homologous chromosomes. One copy is inherited from the mother, the second one from the father. According to autosomal dominant type of inheritance the presence of inborn mutation in a single copy of the gene leads to disorder [3]. This is true in the case of proto-oncogenes, e.g. mutations in RET oncogene predispose to MEN2 syndrome. In the majority of cases, malignancies are caused by mutations of the tumour suppressor genes such as *p53*, or DNA repair genes such as *MSH2*, which show a recessive pattern at the molecular level. Carriers of these mutations develop cancer due to somatic inactivation of the second allele (most frequently deletion) during their lifetime [4-8].
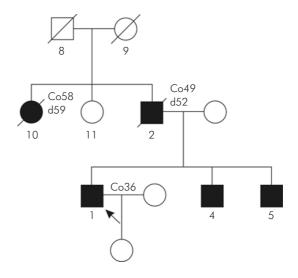
Pedigrees of monogenic diseases with autosomal dominant inheritance are characterised by occurrence of the disorder in all generations (vertical transmission), among men and women, among almost 50% of the relatives [9, 10].

The pedigree of a family with autosomal dominant disease is presented in Figure 1.

In this particular family cancers occur at a younger age in each subsequent generation (so-called anticipation).
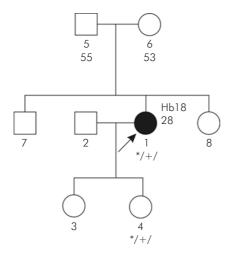
Autosomal dominant inheritance does not show characteristic pedigree features in cases of:
- germline (present in sex cells) mutations arising "de novo" – disease absent among ancestors and siblings of the proband (individuals undergoing genetic counselling); subsequent generations can be affected – Figure 2;
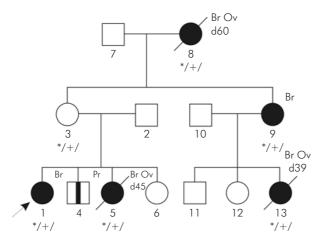

Co36 – colorectal cancer diagnosed at 36
d52 – died at age 52

Figure 1. Family with Lynch syndrome – pedigree features of monogenic autosomal dominant disease

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Hb – haemangioblastoma
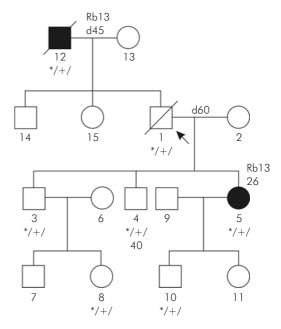*/+/ – individual carrying constitutional mutation

Figure 2. Pedigree of family with disease caused by germline "de novo" mutation within *VHL* gene

d60 – died at age 60
Ov – ovarian cancer
Pr – prostate cancer

Figure 4. Phenocopy – breast cancer unrelated to constitutional mutation in family with *BRCA1* mutation

- mosaic mutation present only in some of the tissues; such alterations arise in the fetus "de novo" during pregnancy; single individuals in the family are affected; mutation can be inherited only if it is present in sex cells;
- "low penetrance" mutations; penetrance is defined as the proportion of carriers of mutation who develop cancer; in strong cancer familial aggregations it reaches 80-90%, but in cases with

d45 – died at age 45
Rb13 – retinoblastoma diagnosed in 3rd year of life
*/+/ – individual carrying constitutional mutation

Figure 3. Pedigree of family with low penetrance *Rb1* gene mutation

low penetrance mutations it is much lower, and thus single individuals only are affected [11-15]; an example is presented in Figure 3;
- mutations predisposing to disease occurring among one gender only, e.g. mutations of the *BRCA1* gene are detected among both males and females, but only women develop ovarian cancer;
- small families with low numbers of relatives.

Evaluation of the pedigree and clinical data of families with aggregations of cancers should exclude phenocopies (accidental malignancy not related to mutation responsible for the aggregation of malignant tumours) [16-18]. Figure 4 shows an example of a family with 4 breast cancers caused by *BRCA1* mutation and one breast cancer in a woman without *BRCA1* mutation.

Polygenic predisposition to cancer

In polygenic type of inheritance single individuals are usually affected.

As the results of the studies performed in our centre panels of DNA mutations/polymorphisms, which increase the risk of malignancies, were identified in over 90% of unselected breast cancers (96% of cases with BC diagnosed over 50, 99% of lobular cancer cases – Tables 1-3), 89% of colorectal cancers, 72% of

Table 1. Frequency of identified panel of markers in unselected breast cancers and controls [9]

Gene/Marker	Cancer	Controls
BRCA1	2.7% (26/977)	0% (0/977)
CHEK2	11.9% (113/951)	6% (59/977)
p53	10.1% (85/838)	5.7% (52/918)
TNR	55.6% (419/753)	45.8% (397/866)
FGFR – GG	18.3% (61/334)	13.9% (65/469)
CDKN2A	7% (19/273)	5.4% (22/404)
XPD – GG	41% (104/254)	36.4% (139/382)
XPD – CC/AA	17.3% (26/150)	14% (34/243)
BRCA2	7.3% (9/124)	4.8% (10/209)
XPD – AA	20% (23/115)	18.6% (37/199)
Any marker	**90.6%** (885/977)	**83.4%** (815/977)
Statistic	P=3 × 10⁻⁶	

Table 2. Frequency of identified panel of markers in lobular carcinoma and controls [9]

Gene/Marker	Cancer	Controls
BRCA1	0.7% (1/140)	0% (0/140)
CHEK2	19.4% (27/139)	4.3% (6/140)
p53	10.7% (12/112)	6% (8/134)
BRCA2	9% (9/100)	4.8% (9/126)
FGFR – nAA	75.8% (69/91)	60% (72/120)
TNR	72.7% (16/22)	39.6% (19/48)
NOD2	16.7% (1/6)	0% (0/29)
M3K – nAA	80% (4/5)	41.4% (12/29)
Any marker	**99.30% (139/140)**	**87.90% (123/140)**
Statistic	P=0.00073	

Table 3. Frequency of identified panel of markers in all breast cancers diagnosed at age above 50 and controls [9]

Gene/Marker	Cancer	Controls
BRCA1	2.1% (14/667)	0% (0/667)
CHEK2	11% (72/653)	4.8% (32/667)
p53	11% (64/581)	5.4% (34/635)
TNR	55.9% (289/517)	45.3% (272/601)
FGFR – nAA	68.9% (157/228)	60.8% (200/329)
BRCA2	5.6% (4/71)	2.3% (3/129)
XPD – CC/AA	13.4% (9/67)	6.3% (8/126)
NOD2	13.8% (8/58)	6.8% (8/118)
XPD – GG	48% (24/50)	35.5% (39/110)
Any marker	**96.1%** (641/667)	**89.4%** (596/667)
Statistic	P=2.4 × 10⁻⁶	

malignant melanomas, 36% of ovarian and 27.5% of prostate cancers [19]. DNA alterations associated with "moderate" risk may have a significant clinical impact.

Associations of "moderate risk" mutations and polymorphisms of many genes and additional influence of environmental factors can significantly increase the risk of cancer development in individuals carrying these alterations. Accumulation (linear association) of the

DNA alterations can be identified when the total risk of cancer is the sum of risks of single DNA alterations, e.g. total risk of cancer development increased twofold in compound carriers of two mutations in genes A and B (both mutations associated with 50% increased cancer risk). In other cases a non-linear association (interaction) can be diagnosed (e.g. total risk increased fivefold in compound carriers of the previously mentioned mutations of genes A and B [20]).

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