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Selected genetic factors increasing risk of neoplasia

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Abstract

Introduction: Neoplasia is defined as abnormal and excessive growth of selected tissue. Several factors, such as mutations in selected genes, can increase the risk of cancer expansion in human body. The aim of the article is to review the selected genetic factors which increase the risk of neoplasia and results of their presence in the human body.

Material and methods: Articles in the Google Scholar, Pub Med database have been analysed using keywords: cancer, neoplasia, genetic factors, driver genes, cancer transformation, older people.

Results: The aim of several genes is repairing damaged or dysfunctional DNA and preventing cells from abnormal or excessive. Mutations in selected genes cause inhibited production of the gene protein product or a change in its function, which increase the risk of neoplasia. The presence of mutated genes results in the initiation of the process leading to expansion of cancer cells in selected tissue. Moreover, a genetic mutation can lead to syndrome of tumors occurring in several organs. However, the increasement of cancer risk is related to numerous mutations, whereas the minority of carcinomas occur because of congenital gene defect and the majority is caused by environmental factors which contribute to creating various mutations.

Conclusions: Thanks to the development of genetics in the field of medicine and introduction of genetic tests, the process of diagnosis of several tumors and syndromes is more efficient than in the past. The occurrence of mutation in genes, such as BRCA1, BRCA2, VHL, MSH2 and MLH1 and many more, relates to presence of selected tumors. By the introduction of pharmacogenetics, dozens of molecular-targeted drugs are used in the treatment of several types of cancers leading the achievement of therapeutic success. Nevertheless, the genetic background of many types of cancers is unknown and needs further study, as well as drugs targeting at selected genes mutations requires more development and guidelines in the treatment process.

Keywords: cancer; neoplasia; genetic factors; driver genes; cancer transformation; older people;

Introduction:

Cancer is a generic term for a large group of diseases characterized by the growth of abnormal cells beyond their usual boundaries that can then invade adjoining parts of the body and/or spread to other organs. Other common terms used are malignant tumours and neoplasms. Cancer can affect almost any part of the body and has many anatomic and molecular subtypes that each require specific management strategies.

Cancer is the second leading cause of death globally and is estimated to account for 9.6 million death in 2018. Lung, prostate, colorectal, stomach and liver cancer are the most common types of cancer in men, while breast, colorectal, lung, cervix and thyroid cancer are the most common among women [1].

Cancer arises from the transformation of normal cells into tumour cells in a multistage process that generally progresses from a precancerous lesion to a malignant tumour. These changes are the result of the interaction between a person's genetic factors and 3 categories of external agents, including:

- Physical carcinogens, such as ultraviolet and ionizing radiation;
- Chemical carcinogens, such as asbestos, components of tobacco smoke, aflatoxin (a food contaminant), and arsenic (a drinking water contaminant); and
- Biological carcinogens, such as infections from certain viruses, bacteria, or parasites [3].

A mutation is a change in a genetic sequence. Mutations include changes as small as the substitution of a single DNA building block, or nucleotide base, with another nucleotide base. Meanwhile, larger mutations can affect many genes on a chromosome. Along with substitutions, mutations can also be caused by insertions, deletions, or duplications of DNA sequences.

Some mutations are hereditary because they are passed down to an offspring from a parent carrying a mutation through the germ line, meaning through an egg or sperm cell carrying the mutation. There are also non hereditary mutations that occur in cells outside of the germ line, which are called somatic mutations. Mutations can be introduced due to mistakes made during DNA replication or due to exposure to mutagens, which are chemical and environmental agents that can introduce mutations in the DNA sequence, such as ultraviolet light. Some mutations do not result in changes in the amino acid sequence of the encoded protein and can be described as silent mutations. Other mutations result in abnormal protein products. Mutations can introduce new alleles into a population of organisms and increase the population's genetic variation [2].

Cancer is caused by two general factors:

1. Internal factors such as inherited mutations, hormones, and immune conditions

2. External/environment/acquired factors such as tobacco, diet, radiation and infectious organisms

All cancers are a result of multiple mutations. Only 5–10% of all cancers are due to an inherited gene defect. 90-95 % of cancers is arised from environmental factors, but all of environmental factors cause the acquisition of cell mutations [4].

Cancer is a typical example of a multigenic disease, which means that the cause of cancer is simultaneous damage in many genes. Synchronous damage to many of the processes carried out by the cell leads to the loss of homeostasis. Transforming a healthy cell into a cancer cell requires the appearance of several to several dozen genetic damage at one time. In addition, genetic damage must refer to the so-called driver genes, only changes in this group of genes are able to change the healthy cell into a cancer cell. We can not forget about passenger genes that affect the tumor phenotype, but independent gene damage from this group is not able to initiate the process of carcinogenesis. The driver genes is relatively small, in different types of tumors their role may have a different meaning, that is, the driver genes in one type of cancer are driver genes and in others are passenger genes. Similarly, the case looks like passenger genes. An interesting phenomenon is the diversified ability to induce the process of tumorigenesis of the same driver genes, for example mutations in BRCA1 are a stronger activator of carcinogenesis in breast cancer than in ovarian cancer or prostate cancer. Unfortunately, we can not choose the genome we inherit but for this we can identify genetic changes in our genome that increase the probability of cancer transformation.

Searching for causes of familial occurrence of a specific type of cancer has led to the separation of a group of genes called susceptibility genes, the occurrence of mutations in these genes increases the risk of developing a specific type of cancer. Susceptibility genes, depending on how much they increase the probability of falling ill, are divided into:

- Genes with high penetration
- Genes with average penetration
- Genes with low penetration

Genes with high penetration increase the risk of getting close to unity, and genes with average penetration several times. Genes belonging to these two groups belong to the driver genes but their involvement in cancer transformation is of secondary importance, because the most important cause of carcinogenesis is lifestyle. Low penetration genes are usually polymorphic variants of detoxification genes, for example NOD or GST. Most susceptibility genes are suppressor genes, their damage leads to uprising defective products that interfere with cell homestasis by affecting DNA repair mechanisms, cell cycle regulation, differentiation or apoptosis. Not many susceptibility genes are proto-oncogenes, their damage increases the risk of cancer development, because they are activating mutations that directly or indirectly affect the signal transmission in the cell.

The implementation of a subpopulation of healthy people, in whom genetic and molecular studies have detected genes that increase the risk of cancer for medical surveillance would increase the effectiveness of screening tests and clearly reduce the cost of medical care. Treatment of neoplastic diseases should be strengthened by molecular examination of the disease in order to maximize the personalization of the treatment - treatment to the molecular subtype of the disease and treatment taking into account individual variability in the metabolism of drugs - pharmacogenomics [5].

BRCA1 and BRCA2 genes

BRCA1 is a human gene encoding protein called BRCA1 (Breast cancer type 1 susceptibility protein). Location of this gene is on the long arm of chromosome 17 (17q21) [6]. Length is 81097 base pairs and contains 24 exons[7,8].

Product of BRCA1 gene expression is protein, as mentioned before, called BRCA1 (the same as the gene) consisting of 1873 amino acids residues [6].

There are four major domain in this protein: Znf C3HC4- RING domain at the N-terminal region, the BRCA1 serine domain, two BRCT at the C-terminal region. BRCA1 protein is expressed in mainly breast cells (and other tissues) and is responsible for repairing damaged DNA and causing apoptosis of a cell if damage cannot be repaired [9].

BRCA1 protein plays an important role in repairing double-strand breaks (DSBs) in DNA. It is a part of protein complex responsible for fixing DNA when double-strands are broken. It is difficult to replace broken parts of DNA when both of strands are damage since there is no matrix strand that this protein complex can use to copy and repair with base complementary rule. Therefore BRCA1 protein assist homology-directed repair (homologous recombination - HR) which copy a sequence from intact sister chromatid. In this process in the nucleus BRCA1 protein binds with RAD51 protein during the repair [10].

BRCA1 protein also participates in activation of cell cycle checkpoints. Cell cycle checkpoints are used to supervise the chromatin status during cell cycle. If there is damage in the DNA, then cell cycle checkpoints are activated and prevents cell from proceeding to replicate. That gives time for protein repair complexes to fix damages in DNA before duplication of DNA [11].

BRCA2 gene is located on chromosome 13 in positions 12.3 on the long arm (q) - (13q12.3). It contains 27 exons. Length is 84 792 base pairs [13].

BRCA2 gene encodes protein BRCA2 (Breast cancer susceptibility protein 2) formed by 3 418 amino acids. Similar to BRCA1 protein, BRCA2 protein expression occur mainly in breast cells (but in other cells as well) and also participates in forming genomic stability and help fixing DNA damage [14].

As mentioned before, despite different origin and structure of BRCA2 and BRCA1 protein, they function in similar manner, both binds to RAD51 protein and plays a role in homologous recombination. The BRCA2 protein is key part of HR. When it binds to RAD51 protein it enhance recombinational DNA repair by promoting congregation of RAD51 onto single-stranded DNA [15]. Its is worth to mention that in order to assembly RAD51 to DNA DSBs a formation of BRCA1-PALB2-BRCA1 complex is required [16].

Mutations in either of mentioned genes lead to increased risk of breast and ovarian cancer and may produce hereditary breast-ovarian cancer syndrome (HBOCS). There are hundreds of types of mutations that have been detected in those genes, some are harmful, while others have no proven impact. There are also possibility of single nucleotide polymorphism which may higher risk of cancer by a small amount or only in certain circumstances [17].

Estimated 12% of women in overall population will develop breast cancer in their lives. On the contrary, 72 % of women with BRCA1 and 69% of women with BRCA2 mutation will have breast cancer by the age of 80. Similar tendencies are visible in ovarian cancer with 44% of women with BRCA1 mutation developing ovarian cancer and 17% with BRCA2, in contrast to 1.3 % women having an ovarian cancer in overall population at some point in their lives [18].

There is no surprise why those number are that high. High-risk mutations disable proper function of BRCA1 and BRCA2 genes that leaves cells with damaged DNA without possibility to repair that cause them to be prone to develop cancer.

Interestingly some populations are more susceptible to cancerogenesis than others. This has to do with founder effect. This effect occur when a population is established with small number of individuals and that cause certain genetic traits to prevail in population, there BRCA1 and BRCA2 gene mutations [19]. The proven groups with higher prevalence of harmful mutations are for example Ashkenazi Jews or when it comes to Europeans, in Norwegians, Danes or Icelanders [18].

We know from the description of function above what role BRCA1 and BRCA2 proteins play in cells, thus we may predict and observe what effects on cells will have mutations that impair functions of those proteins.

Mutated cell will be unable to perform error-free repair process - homology directed repair, therefore cell is left with genetic disorder that may lead to breast or other types of cancer. Furthermore activation of cell cycle checkpoints will be impaired which might cause that previously damaged DNA will be conveyed to child cells and that increases chances of cancerogenesis as well, but it seems it is only an issue in cells with BRCA1 gene mutations, because BRCA2 protein doesn't have clear effect on cell cycle checkpoint enforcement. In addition there can be problems with modulation of chromatin and DNA structure in mutated cells which probably could have a negative effect on accessibility of DNA changes to repair mechanisms, but more research has to be conducted on this subject.

At the end it has to be acknowledged that those difunctions are mainly in BRCA1-deficient cells, because despite involvement of BRCA2 protein in repairing damaged cell DNA is certain, the functions of BRCA2 protein is not as marked as those of BRCA1 protein, and yet more research is necessary [20].

VHL gene

VHL gene is located on the short arm of chromosome 3 (3p25.3) and include 4 exons. Exact location starts at 10141635 and ends at 10153670 bp from pter [21,22,23,24]. The highest expression is in lymph node and spleen. It also appear in brain,, kidney, lung and many more organs[25].

VHL encode two isoform of protein: pVHL30 (30 kDa and 213 amino-acid), pVHL19 (19 kDa and 160 amino-acid). There is currently 761 different types of VHL described mutation [26]. Both gene products have tumor suppressor activity in vivo [27]. Protein VHL is aggregating with elongin C and elongin B to form VCB complex. It then incorporate cullin 2 (CUL 2) and the RING finger protein RBX1 creating more complex structure called VCB-CR complex, which is in charge of ubiquitylation and proteasomal degradation of HIF1α (hypoxia-inducible factor 1α) in normoxia [28]. HIF1α together with HIF1β bind to enhancer called a hypoxia response element that appear in many genes activated while oxygen deficiency such as VEGF ,glycolytic enzymes, erythropoietin.

Absence or inappropriate function of pVHL in VCB-CR complex causes angiogenesis, erythropoiesis and greater contribution in anaerobic metabolism, by not forming complex which degrades HIF1α [29]. Furthermore pVHL most likely play a role in other cellular functions such as microtubule stabilization, maintenance of the primary cilium, regulation of apoptosis, controlling of cell senses, degradation of TGFα, LYT 10, TGF β, carbonic anhydrases CA9 and CA12.Products of VHL gene also allow cell to exit cell cycle and enter the quiescent state and inhibit hepatocyte growth factor (HGF), which overexpressed can lead to invasion in renal cell carcinoma [24]. Mutation in VHL can also cause increase production of TGFα, which act to stimulate growth of cell within the tumor [30]. Based on this roles VHL is classified as tumor suppressor [31].

Identification of pVHL role in regulating HIF- mediated cellular resonse to hypoxia, influence today's ccRCC treatment. There are drugs which include multiple tyrosine kinase inhibitors that target VEGF receptors (sorafenib, pazopanib), inhibitor of the mTOR

pathway- responsible for cell proliferation (temsirolimus, everolimus) and the monoclonal anti-VEGF antibodies (bevacizumab) [32]. So far there aren't any studies which unequivocally states that the presence or absence of mutation might provide useful biomarker in ccRCC. However it is caused by insufficient number of studies because effective treatment options have come into widespread use only recent.

MSH2 gene

MSH2 is a tumor suppressor gene that encodes post-replication DNA mismatch repair protein called MSH2. It is characterized by two locations, i.e. cytogenetic and molecular [33]. These two types of localization boil down to one description indicating the area from 47 403 067 to 47 634 501 base pairs (bp) located on the short arm of chromosome 2 between 21 and 16.3 positions (2p21-p16.3)[33,34,35,36]. It is yeast mutator gene homolog (bacterial mutS). The MSH2 gene contains 16 exons that cover the area of 80098 bp. The length of mRNA characteristic for the MSH2 gene is 3145 bp. The described gene has two characterized transcription variants (1 and 2 variants) coding for different isoforms that differ in length [37]. This is due to the lack of the first exon that has a place to start translation, so the first transcript is shorter than the N-terminal side. MSH2 is characterized by nuclear expression. In addition to participating in DNA repair, MSH2 and products encoded by this gene are involved in: oxidative phosphorylation, embryonic development of utero and somatic recombination of immunoglobulin genes. Expression of MSH2 is characterized by tissue specificity observed primarily for: colon, lymph node, testis, thyroid, bone and fetal ovary [36,37]. Overexpression of described gene is also observed in peripheral blood mononuclear cells, melanocytes and CD8 T cells [36]. For example, the expression of this gene in monocytes can causa UV-B-induced cell cycle regulation but also apoptosis [36].

The MSH2 also referred to as the MutS 2 protein homolog is a protein consisting of 934 amino acids. The molecular weight is 104.7 kilodaltons (kDa) [36]. MSH2 contains two interaction domains and one DNA binding domain, for MSH3 or MSH6 and for MutL homologs. The presence of these domains enables the formation of heterodimeric complexes. The MSH2 protein forms two different heterodimers: MutS alpha (MSH2-MSH6) and MutS beta (MSH2-MSH3) (MutS beta). MutS alpha recognizes base-base dinucleotide insertion-deletion loops (IDL) and single base mismatches in a strand of DNA while MutS beta recognizes large insertion-deletion loops up [36,38,39]. MutS alpha and MutS beta forms a ternary complex with MutL which is responsible for strand recognition, excision, and resynthesis [39].

MSH2 and complexes which it forms are primarily responsible for binding DNA mismatches, which initiates the process of genetic material repair. Described mechanism named post-replicative DNA mismatch repair (MMR). It is necessary system to combat genomic damage.

MSH2 is also responsible for recruits DNA helicase MCM9 to chromatin. This causes unwinds of DNA stand which contains DNA mismatch. It comes to then ATP binding and hydrolysis which is necessary in MMR. The most important moment for MutS 2 protein during the whole MMR process is converts MSH2 for a sliding clamp which allows diffusion and repair along the DNA backbone. This is essentials for the initiation and operation of the MMR system [39,40,41]. MutS protein homolog 2 also has many functions specific to the MSH2 gene. As previously mentioned these are oxidative phosphorylation, embryonic development of utero and somatic recombination of immunoglobulin genes but also magnesium ion binding [36]. MSH2 also interacts with various types of proteins [39,40]. The MSH2 protein is part of the MutS family which includes also MSH 1, 3, 4, 5 and 6 proteins. Their expression is observed in eukaryotes but also among archaea and

bacteria [41].

Mutations within the MSH2 gene are most often associated with microsatellite instability. These are short sequence repeats which occurs because these sequences are prone to mistakes during the DNA replication [42]. If the repair systems do not work, duplications or deletions of these sequences arise over time. Excessive accumulation of DNA damage and lack of activity of the MMR system result increasing the quantity of mutations due to error-prone translesion synthesis .This results in more frequent DNA damage and may be responsible for the occurrence of various diseases, among which cancer takes the first place [42,43,44].

Within MSH2 is described over 300 germline mutations. These are not occur in any specific region of the gene and include both insertions/deletions as also nucleotide substitutions (nonsense, missense and splicing errors) [43,44,45].

Most mutations result in the occurrence of tumors, i.e. hereditary non-polyposis colorectal cancer 1 (HNPCC1), acute lymphoblastoid leukemia (ALL), endometrial cancer, mismatch repair cancer syndrome (MMRCS), colorectal cancer (CRC), ovaria cancer, renal cell carcinoma, esophageal squamous cell carcinoma, head and neck squamous-cell carcinoma, hepatocellular carcinoma, gastrin cancer and soft-tissue sarcoma. Many of the diseases listed are also caused by MSH2 promoter methylation [33,34].

Mutations within MSH2 can also cause Lynche syndrome and its wariant - Muir-Torre syndrome but also non-neoplastic diseases such as Takayasu arteritis, chronic kidney disease and Alzheimer's disease [46]. Most mutations within MSH2 cause the above-mentioned disease entities, however described some genetic changes have also been in exons and introns as non pathogenic for organism [46].

The most common condition associated with the mutation within MSH2 is HNPCC1. It is a disease of an autosomal dominant character. The most characteristic for this disease is Replication ERror phenotype (RER+). Presence of mutations in the MSH2 gene resulting in HNPCC1 is characterized by predisposition to early-onset extra-colonic tumors of the gastrointestinal, colorectal carcinoma and cancer both urological as also female reproductive tracts. HNPCC is divided into two subgroups. Type 1 is associated primarily with predisposition to proximal colon cancer. While type 2 is responsible for increased risk for many types of cancers within uterus, breast, ovary, stomach, skin and small intestine. Mutations of MSH2 contributing to HNPCC account for about 25% of all examples of genetic material abnormalities in this area. These mutations are germline Mutation occurs in one of the alleles and the loss of heterozygosity (LOH) gives the mutations causing HNPCC1 a dominant character. More over HNPCC1 can be caused by MicroSatellite Instability (MSI) [46,47,48]. In most cases, MSH2 related diseases are caused by different types of mutations. However, also reduction of MSH2 expression can lead to cancer such as non-small cell lung cancer (NSCLC) [46,47,49].

MLH1 gene

MLH1 is a tumor suppressor gene which is responsible for coding the protein playing a major role in DNA repair. The cytogenetic location of MLH1 gene is short arm of chromosome 3, in band 22 counting from the centromere, in sub-band 2. It was determined with fluorescence in situ hybridization [55]. This gene is located between 36.993,350 and 37.050.846 base pairs [50].

MLH1 is one of the genes responsible for mismatch repair (MMR). The human *MLH1* gene is a homologue of the E. coli MutL gene specially in the N-terminal region. Orthologs *MLH1* is observed among 274 organisms highlighting e.g. mouse and yeast *Saccharomyces cerevisiae*. *MLH1* takes part in protein-protein interactions during the differentiation of DNA strands and their removal. Also participates in recognizing non-

compliance with nitrogen bases. This gene encodes a protein of the same name, or MLH1, which has 9 isoforms. Most of them perform similar functions to the transcription variants corresponding to the MSH2 isoforms. The differences are based on lack of one of the exons in option 6, which leads to frameshift. or presence of ATP-binding proteins such as histidine kinase, topoisomerases, heat shock protein HSP90, DNA gyrase B, phytochrome-like ATPases and DNA mismatch repair proteins [51,52]. MLH1 includes 19 exons located in the area of 57360 bp, which answers approximately 100kb. Additionally, exons 1 to 7 have a region that is highly conserved in the MLH1 and PMS1 genes of yeast [55] .The length of the gene is in the area from 6993350 and ends at 37050846 bp. Moreover, length of transcribed mRNA for this gene is 2524 bp [53]. Overexpression of described gene is observed in colon, breast, lung, lymphocytes, spleen, prostate, thyroid, testis, gallbladder and heart [54].

The MLH1 also known as MutL homolog 1 is a protein whose molecular mass is 84.6 kDa. This protein contains 756 aminoacids [53]. The MLH1 gene contains an ATPase (Adenosine triphosphate) domain but also two domains whose heterodimerize with MutS homologs (MSH2, MSH3, MSH6) and MLH3, PMS1 or PMS2.

After binding with PMS2 a heterodimer MutLα is formed. It is responsible for the recruitment of the proteins whose are needed for the excision and repair synthesis. MLH1 is a protein that has no catalytic properties [53]. MutLα can interact with MutSβ. Then, the PMS2 subunit present in the complex formed breaks the single strand of DNA near the DNA mismatches, which provides a starting point for exonuclease degradation. MutLα can also heterodimerize with MLH3. A complex called MutLγ is created then which involved in meiotic crossing over.[51]. MutLγ heterodimer is necessary for the passage of oocytes through metaphase II of meiosis [56].

Based on the above information, can be distinguish several groups of proteins with which MLH1 interacts. Expression of MLH1 is presents for 27 different tissues but overexpress is observed in testis, thyroid, lymph node and heart.) At the cellular level, high activity is observed within the cell nucleus (in particular in chromosomes) [52].

MLH1 is part of the BRCA1-associated genome surveillance complex (BASC) and RAD50-MRE11-NBS1 protein complex. MLH1 protein interacts with subunits of DNA polymerase III. It plays an important role to recruit the DNA polymerase III for the site of the MMR. MLH1 engages in signaling damage to the genetic material, which results in the arrest of the cell cycle and the induction of apoptosis in case of major DNA damages [52]. The activity of MLH1 protein is also observed in chromatin binding, guanine/thymine mispair binding, isotype switching, meiotic spindle midzone assembly, meiotic telomere clustering, response to bacterium, somatic hypermutation of immunoglobulin genes, spermatogenesis and synapsis activity [54].

Mutations in the MLH1 gene result from microsatellite instability. Their formation leads to inhibited production of the MLH1 gene protein product or a change in its function. The effect of this is the increase and accumulation of errors in the DNA created during cell division, which leads to malfunctions of the cell leading to neoplastic transformation. Mutations in the MutL gene mainly occurring in the ATP-binding site because MutL is responsibles for bind and hydrolyzes ATP to ADP and Pi [55][62].

Mutations occurring within MLH1 are in the form of nucleotide substitutions (nonsense, missense, splicing errors) and insertions/deletions. The MLH1 protein resulting from the mutation has the most abbreviated structure [53].

The result of mutations is mostly hereditary non-polar colorectal cancer (HNPCC), also referred to as Lynch syndrome. It is a dominant autosomal disease associated with an increased risk of colon cancer. It arises due to the excision of 16 or 6 exons. About 50% of all cases of Lynch syndrome are associated with hereditary mutations in the MLH1 gene.

Lynch syndrome is associated not only with colon cancer, but also with an increased risk of ovarian cancer, endometrial cancer, liver, small intestine, gallbladder, brain and upper urinary tract [62].

It is important to reduce the expression or silencing of DNA repair genes resulting from the methylation of the MLH1 gene promoter region and miR-155 overexpression. This may result in stomach cancer, esophageal, Head and neck squamous cell carcinoma (HNSCC), Non-small cell lung cancer (NSCLC) or colorectal cancer. Disorders within the MLH1 gene can also contribute to the occurrence Turcot syndrome which is associated with an increased risk of glioblastoma occurrence [62].

Discussion

The development of genetics, which resulted in the recognition of the human genome and its various variations - mutations and polymorphisms, contributed to the discovery of the causes of many genetic diseases. The development of this branch of science has also allowed the discovery of predictors and prognostic factors of various diseases.

Thanks to the development of pharmacogenetics, dozens of molecular-targeted drugs are created every year, and a large part of them is used in the treatment of cancer. Most often, cancerous mutations are associated with excessive activity of proteins formed from mutated genes. This results in a disruption of the signaling pathways and this disturbs the homeostasis of the cell. In this case, blocking the mutant signaling pathway causes suppression of tumor cells. Many tumors show heterogeneity which prompts you to look for new drugs.

Thanks to genetic tests, it is possible to detect both mutations conditioning sensitivity to targeted therapies and detection of resistant cells for this type of treatment. Without genetic testing, it is not possible to qualify patients for molecular-targeted therapy [63].

Genetic testing is also used to detect mutations that cause non-cancer diseases such as hemochromatosis, Crohn's disease, etc., but genetic tests in oncology are the most useful and used on the largest scale. According to the recommendations of the global oncology societies, the most common mutations in oncology should be determined in common clinical practice [64].

Currently, apart from the classic histopathological classification of tumors, more and more cancers also receive molecular classifications. About 20 molecular markers are currently accepted by the European Society for Medical Oncology for gastric, prostate, breast, lung and colorectal cancer as properly documented so that they can be used in clinical practice.

Personalized treatment is now directed towards the driver genes. In this way, molecular diagnostics has been included in the diagnostic part of cancer [65].

The statement of a mutation can have a significant impact on the course of the disease, and thus the fate of the patient and his family. Errors and lack of standardization of genetic tests can have disastrous consequences. Therefore, conducting genetic research requires strict legal regulations. In the European Union, regulations are set by individual countries. In the European Union there is a EuroGentest institution financed by the European Union, which deals with the design of legal regulations and the control of tests available in Europe. In Poland, the law regulating the legal issues of genetic testing has not been adopted so far [64].

In Poland, it is difficult to talk about the development of modern personalized medicine in oncology due to the lack of legal regulations for genetic testing, lack of genetic and oncological diagnostic infrastructure, lack of detailed standards of genetic testing and lack of appropriate funds for diagnostics by the National Health Fund. Lack of expenditure

on laboratories operating within the national health care system may lead to the inhibition of activities and the development of laboratories.

Lack of state supervision and quality control of genetic diagnostics provokes clients (hospitals, oncology clinics) to use cheaper services performed by laboratories, not subject to any supervision, or send patients' DNA abroad [65].

However, the development of genetics-related branches of science significantly increases the possibilities of personalized treatment of cancer. However, this development creates new challenges. Such as developing standardized genetic tests, performing tests in laboratories equipped with appropriate diagnostic equipment. In addition, steps should be taken to establish a transparent system for the control of genetic laboratories and the validation of methods used by them, as well as a good system for financing genetic testing. A permanent update of test recommendations and genetic laboratories is required based on the latest guidelines [63].

Conclusions

Cancers are huge problem for global public health and one of the leading causes of deaths especially in highly developed countries where we observe an increase in life expectancy. There are multiple factors causing carcinomas – they may be divided into three groups: physical, chemical and biological. We also distinguish the simplest division into internal (for example inherited mutations, endocrine disruptors) or external causes (radiation, diet, lifestyle etc.). In this work selected genetic factors increasing risk of neoplasia were described. It is worth to mention that all cancers are a consequence of numerous mutations, however minority of carcinomas occur because of congenital gene defect. Significant majority of cancers is caused by environmental factors which contribute to creating various mutations.

First of all, BRCA1 and BRCA2 were described. Function of these proteins is similar, however they are not related. They were mentioned together because they are both associated with higher risk of breast cancer. Furthermore, mutations of BRCA1 and BRCA2 genes are connected also with developing ovarian cancer. Mentioned mutations appear more often in certain populations like Ashkenazi Jews or Scandinavians like Icelanders, Danes or Norwegians.

Next, VHL gene mutation was outlined in a similar way to two previous mutations. This gene plays a part in many cellular activities like regulation of apoptosis or microtubule stabilization. It is worth noting that it is classified as a tumor suppressor, because it enhances the degradation TGF alpha, nevertheless mutations in this gene stimulate growth of neoplastic cells inside the tumors. Renal cell carcinoma is associated with VHL gene mutation.

MSH2 gene mutations are mainly connected with microsatellite instability which leads to many diseases and cancer is the most common one. Results of this mutation are for example hereditary non-polyposis colorectal cancer 1, acute lymphoblastic leukemia, endometrial cancer and soft-tissue sarcoma. Besides tumors mutations of described gene can also cause vascular diseases like Takayasu arteritis or neurodegenerative one - Alzheimer’s disease.

Last but not least, MLH1 gene is also tumor suppressor like VHL outlined earlier. At the cellular level its mutations lead to microsatellite instability what also was mentioned in the description of MSH2 gene. It is also connected with 50% of cases of Lynch syndrome (which is also caused by mutations of MSH2 gene), which causes increased risk of colon cancer. However in this syndrome, there may appear tumors in different organs for example: ovary, gallbladder or brain. Furthermore, its mutations also may lead to non-small cell lung carcinoma, stomach cancer or colorectal cancer.

To conclude, genetic factors increasing risk of neoplasia are scientifically and medically very important subject. Thanks to the development of different branches of biomedical sciences we know much more about neoplasia. Nevertheless, there is still much more to discover and describe. The more we know about mutations causing neoplasia, the better we get to know „the emperor of all maladies" - cancer.

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