

THE IMPORTANCE OF THE HEREDITARY RISK FACTORS IN THE NEOPLAZIC DISEASE

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Abstract: During lifetime, cancer risk is an individual risk and depends of our genetic luggage. Breast cancer is an example in which immediate relatives may have a higher risk of breast cancer or other types of cancer. Sometimes the increased risk may be due to a genetic mutation. BRCA1 and BRCA2 are examples of genetic mutation that give rise to the increased risk of breast cancer. Women with these mutations also have significantly higher risk of developing ovarian cancer. Most of the familial cancers are multi-factorial and most of the times, there are no demonstrable genetic markers or patterns. The pattern of familial clustering occurs more in certain cancer types, such as: breast cancer, colon cancer, and ovarian cancer. Genetic testing is now possible and important for assessing the risk of cancer.

Keywords: genetic testing, breast cancer, BRCA

Rezumat: Depistarea formelor de cancer cu predispoziție genetică este o preocupare primordială a medicinei contemporane. Testarea genetică pentru genele BRCA este deja o practică în aprecierea riscului de cancer mamar. Detectarea acestor cazuri va impune o atitudine corespunzătoare de prevenire a apariției tipului de cancer la care este predispusă persoana sau, prin controale periodice specifice, depistarea precoce în stadii puțin avansate, în care rezultatele terapeutice sunt mult mai bune.

Cuvinte cheie: testarea genetică, cancerul de sân, gena BRCA.

INTRODUCTION

The ideal strategy for fighting against cancer is prevention and this is possible by knowing the risk factors. More and more studies bring new evidence to demonstrate the incidence of certain hereditary risk factors.

PURPOSE OF THE PAPER

The importance of knowing the hereditary risk factors in the neoplazic disease. Heredity increases the cancer risk in many types of cancer: breast cancer, prostate cancer, colon and rectum cancer and the gastric cancer. A series of genetic alterations are associated to an increased risk for the development of a neoplasia. This possibility varies between the different types of tumours.

MATERIAL AND METHOD

Examples of cancers associated with hereditary risk factors.

Heredity represents a risk factor for the development of the colon and rectum cancer in both genders. A positive family history regarding the colon-rectum cancer and/or other neoplasiae increases the risk for the development of the colon-rectum cancer 2,6 times in women and 3 times in men. The genetic, epidemiologic and experimental studies suggest that the occurrence of the colon and rectum cancer is the result of the complex interaction of the environment factors and the genetic susceptibility. The efforts for the identification of the causes and the prevention measures suggested that the adenomatous polyps are precursors for a large number of colorectal cancer and the measures for decreasing the polyps' incidence led to a decrease of the colorectal cancer risk.

The hereditary colorectal cancer is a genetic disease which is developed as an evolutive process. Regarding the sporadic forms, the initial genetic injury occurs spontaneously or it is induced by the environment agents into the genome of a single colonic stem cell, thus gaining a proliferative advantage against the surrounding cells. A clone is formed, that is a cellular population within which all cells have the same genomic constitution and implicitly the same genetic anomalies. Genetic modifications occur at its level and each characteristic of a sub-clone evolves in the detriment of the initial one – clonal evolution. The same molecular alterations may exist in the genome of the germinal cells, situation in which hereditary cases of colorectal cancer may occur in the descendents. The molecular study and the introduction of the precocious diagnosis methods radically changed the understanding of the colorectal oncogenesis and allowed the individualisation of many ethiopathogenic forms with particular problems regarding the diagnosis and prevention. The hereditary colorectal cancer may be classified as being polyposic and non-polyposic.

Generally, each disease is considered the result of the interaction of the unique genetic constitution of the individual and the action of the environment factors. The molecular bases of the genetic individuality are represented by the totality of the genes which form the human genome; the analysis of the human chromosomes

allowed the establishment of the “human genome map”, which indicates the locus of the gene and its function, very accurately. Any changes will have as a result the occurrence of certain mutant genes which will be clinically expressed at the phenotypic level

The role of heredity in certain cancer forms has been researched for a long time. A recent study confirms that the colon neoplasm is genetically transmitted, showing that the brothers and sisters of a person suffering from this type of cancer present a risk up to 7 times higher of being touched by the same disease. With a view to study the genetic factors regarding the familial colorectal cancer forms, a group of Swedish researchers gathered information from the national health registry about 10,3 million of people. Mainly, they analysed the brothers and sisters of the patients suffering from colon cancer and they observed that there is a higher risk both in their parents and in their offsprings, in relation with the general population. This risk was estimated to 74%-84%, according to cancer localisation. The brothers and sisters present a higher risk of developing the same disease, especially regarding the tumours located at the level of the right colon. Even if heredity plays an important part in the occurrence of the colon cancer, we should not forget the other risk factors charged with the colorectal cancer.

The American Society of Clinical Oncology (ASCO) established in 1996 that the direct genetic testing is indicated especially in the patients coming from families where cancer clearly proved its predisposition and for whom the result of this testing significantly changed the type of the awarded medical assistance.

The hereditary cancers are those cancers which are transmitted taking into account the Mendelian pattern. Their identification is extremely important, because the risk of cancer occurrence in the affected families is high: 50% in the case of the dominant autosomal transmission and 25% for those autosomal recessive. For example, the mutations of the BRCA1, BRCA2 and of other BRCA genes were associated with the risk of the breast cancer and are responsible, in the opinion of some authors, of 5% of the breast cancers. In other situations, the large number of the neoplasms from certain families sustains the genetic predisposition, but these are not transmitted according to Mendel's laws. They are called familial cancers.

Another category of neoplasms is that of the neoplasms without familial aggregation but with evident genetic predisposition. This is characterised by genetic alterations causing cancer predisposition due to an unusual sensibility to environment carcinogens. This sensibility is due to the genetic factors which determine, a certain way of metabolization of certain carcinogens. Thus, in the case of the bronchopulmonary neoplasm, the active smoking represents the cause of 85 % - 90 % of the illness cases and the risk associated to the genetic factors is reduced.

The risk of the bronchopulmonary cancer is 30 times higher in smokers than in the non-smokers, but not all those smoking may develop the disease, as the

metabolization of carcinogens of the cigarette's smoke may be influenced by the genetic variation of the enzymes which detoxify these noxious agents.

Recent studies proved that neoplasiae are determined by a genetic disorder. Cancer is a clonal malady because all the cells of a tumour came from the same cell where the proliferation regulation mechanisms were affected.

Women presenting mutations of the BRCA genes present a higher risk for breast cancer. A familial predisposition is also presented in 30% of the gastrointestinal tumours.

Regarding these cases, it is important to differentiate the hereditary gastrointestinal cancer – inherited and a familial clustering of the gastrointestinal cancer cases.

During lifetime, the women carrying mutations of the BRCA 1 and BRCA 2 genes presented the risk of breast cancer in percentage of 56% - 87%, in comparison with 10% - 12% of the general population; the breast cancer in these patients tended to appear at early ages. The mutant BRCA1 genes are also involved in the indirect ovarian cancer, interfering with the biochemical signals through which the communication between the ovarian cells is achieved. BRCA1, the gene of the breast cancer, not only it determines the breast cancer in four or five women carrying the mutant form, but it also determines a risk of 40% regarding the occurrence of the ovarian cancer until the age of 70.

The hereditary luggage of an individual may influence the effect of other environmental or behavioural carcinogen agents. Lately, the notion of cancer as a genetic disease has become more and more evident by the multiple mutations produced by different carcinogens, as well as by observing that the genetic deficiencies of the enzymes involved in the recovery of the RNA injuries are associated with an increased cancer risk. When sufficient mutations regarding the number and their positioning in the genome occur within the germinal line, cancers which are inherited similar to other genetic anomalies may also occur. The mutations happen not only in the germinal cells but also in those somatic, being necessary at least two mutations for a malign transformation to take place.

A lot of genetic factors may influence susceptibility in some cancers. The genetic variations of the carcinogens metabolism from an individual to another, together with the differences regarding the recovering capacity of the RNA injuries and the response capacity to the tumoral promoters govern the relative risk of an individual. For example, the carcinogens metabolism from the cigarette smoke is dependent of the variations within the detoxification enzymes concentration. Another example is the association of the bladder cancer with genetic modifications within the acetylation rate, dependent of the transmission of the particular polymorph form of N- acetyltransferase, which intervenes in the metabolization of the aromatic amines.

The immune congenital or gained deficiencies are a well known factor favouring cancer occurrence. The

constitutional immune deficiencies are transmitted by the chromosome X or by the autosomal recessive one.

Out of these affections with an increased risk for neoplasia development, we mention: infantile agammaglobulinemia, Wiskott-Aldrich syndrome, isolated common deficiency of the immunoglobulin A, variable, common immunodeficiencies, Chediak-Higashi disease.

There are also a series of genetic multisystemic syndromes with an increased risk of malign degeneration: *Neurofibromatosis type I*, *Neurofibromatosis type II*, *hereditary Wilms' tumour*, *Danys – Drash syndrome*, *Beckwith – Wiedemann syndrome*, *Li-Fraumeni syndrome*, *Gorlin syndrome*.

There are also other risk factors regarding the oncologic disease, of which we can mention the controllable risk factors such as: smoking, alcohol, fat-rich diet, fibres-reduced diet, exposure to different physical, chemical factors. Other risk factors cannot be changed, such as: race, gender, age, family history. On the other hand, we can say that there are proved risk factors and suspected risk factors which play a part in cancer generation. Also, we may classify the risk factors in factors belonging to us (hereditary factors) and in environment factors. Although many of the risk factors may influence the disease, for many of them, it is uncertainly known whether they are directly responsible for the disease.

CONCLUSIONS

The laboratory tests for the genetic identifications are very important in diagnosis formulation. The risk factors help the physicians to identify the individuals with cancer high risk, intending to reduce this risk and in the situations in which the risk factors cannot be modified; the identification of the disease at its beginning is an advantage for the efficiency of the therapeutic interventions and the avoidance of complications.

The discovery of the cancer forms with genetic predisposition is a primordial preoccupation of the contemporary medicine. The detection of these cases will impose a corresponding attitude for the prevention of the occurrence of the type of cancer the individual is predisposed to, or by specific periodical check ups, the precocious diagnosis in less advanced stages where the therapeutic results are better. Out of the latter category, we notice the hereditary cancers, the familial cancers and the cancers without familial aggregation but with evident genetic predisposition.

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