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The role of genetic counselling in oncology

Agnieszka Stembalska[1], Karolina Pesz[2]

[1]*Department of Genetics, Wroclaw Medical University, Wroclaw, Poland*
[2]*Queen Elizabeth University Hospital, Glasgow, United Kingdom*

All cancers are genetic disorders, but not all genetic disorders are inherited. Most cancers are sporadic, independent events that do not affect other family members. There is a population risk of developing any cancer and it mainly depends on the individual's age and environmental factors. Cancers linked to predisposition syndromes constitute about 5–10% of all cancer cases. Although it is a small group, making the right diagnosis is important, because of the consequences to the individual, his/her relatives and the benefits they can acquire from surveillance, early therapy and/or surgical interventions.

Genetic counselling plays an important role in diagnosing cancer predisposition syndromes. Hereditary cancer risk assessment includes evaluation of personal and family history, as well as other medical and environmental risk factors. Indications for genetic testing, scope of tests, possible results and their consequences for the patient and his/her family should be discussed.

Key words: cancer, predisposition, sporadic cancer, hereditary cancer, genetic counselling

Cancer as a genetic disease

Any malignant tumour might be regarded as a "disease of the genes". Cancer cells harbour a plenitude of gene mutations and/or chromosomal aberrations that lead to the formation of a "cancer genome", substantially different from the "constitutional genome" of an individual. Those genetic alterations constitute the essence of neoplastic development through which the cells acquire the ability to proliferate uncontrollably, evade growth suppressors, immune response and apoptosis, become immortal, induce angiogenesis, infiltrate surrounding tissues and metastasize [1–3].

Sporadic cancers

In most cases, genetic alterations leading to cancer development arise as "somatic events" in the cells of a given organ during an individual's lifetime, and hence cannot be passed on to the next generation (are not inherited). The risk of these acquired changes increases with age and is often connected to environmental, lifestyle or medical factors. The risk of cancer development in another organ depends on another somatic mutation. Those events are independent of each other and the probability is as high as population risk for a given cancer. In these cases we can talk about sporadic cancers. All people have the risk of cancer development, because cancers are relatively common in human populations. Therefore, in the same family there might be more than one case of sporadic cancer. These are independent events. Although in sporadic cancer cases a specific build-up of mutations (changes) in specific genes may be important for treatment or prognosis (personalised treatment) [4–6], these genetic changes cannot influence the risk of cancer in any relatives of an individual who has a sporadic cancer. Each family member has their own risk of cancer development [1–3].

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Hereditary cancers

Some cancers are the result of so called "germline mutations", that is single gene pathogenic variants from reproductive cells in the parent generation that have been transmitted and are present in every cell of an individual. These variants can be passed on to the next generation, so the presence of genetic changes in an individual with cancer can influence the relatives (children).

In such cases we can talk about hereditary cancers [1, 2, 7, 8]. Since it is not the cancer itself that is inherited, rather the susceptibility to cancer, the condition should be referred to as "cancer predisposition syndrome".

A cancer predisposition syndrome means that there is an increased risk of cancer development from the spectrum of cancers associated with a particular gene. An individual who developed a cancer in one organ still has an increased risk of other cancers. For example: a female carrier of a *BRCA1* mutation has an increased risk of breast, ovarian and pancreatic cancers; with male carriers this also includes prostate cancer [9,10]. Although cancer development risk may be much higher than the population risk and tends to increase with a patient's age, it is not the same for all cancers on the spectrum. The risk of developing a cancer from outside the spectrum is as high as in the remainder of the population (population risk).

Because the gene mutation is present in every cell, genetic testing in any tissue (e.g. blood or saliva) detects gene mutations that cause hereditary cancer.

Although cancer patients with inherited susceptibility constitute only 5–10% of all cancer cases, they cannot be neglected considering the magnitude of risk of malignancy development [11–13]. Diagnosing cancer predisposition syndromes is important, despite their rarity, because of consequences to individual patients and their families and the benefits they can acquire from surveillance, early therapy and/or surgical interventions.

In this article, the diagnostic and clinical aspects of cancer predisposition syndromes in the context of genetic counselling are discussed.

Genetic counselling in oncology

The main challenge in a genetic clinic is distinguishing between those individuals (and/or families) with high or moderate cancer risk from those with low risk to appropriately provide genetic testing and management [5, 11, 12].

The most numerous group of patients referred for genetic counselling would be individuals suffering from cancers that are common in the general population (breast, ovarian, colorectal cancers) but in rare instances falling into the category of mendelian inheritance (single gene disorders). Most hereditary predispositions to cancers follow an autosomal dominant pattern of inheritance, with a 50% probability of passing it on to the next generation [12, 14, 15]. It should be underlined that diagnosing a predisposition syndrome means an increased risk of cancer development in an individual, not a diagnosis of cancer itself. Consequently, in the first instance, genetic testing should be offered to an individual with a history of cancer. Only in cases when it is not possible to test a relative with cancer (the individual died or declines genetic testing), should molecular testing be offered to relatives (initially first-degree relatives, and then others). Negative results of genetic testing in healthy individuals (without a proven genetic mutation in a relative) do not exclude a cancer predisposition syndrome due to genetic heterogeneity of such syndromes (mutations in different genes might be responsible for similar cancer spectra), the limitations of methods employed in genetic testing and the current knowledge of hereditary predispositions [8, 16–18].

Diagnosis of hereditary cancer predisposition syndromes is based on pedigree-clinical criteria, different for particular syndromes (currently approx. 50 syndromes) [8, 14, 16]. It is important that in some cancer predisposition syndromes, apart from malignancies, there are also noted multiple benign tumours (examples include MEN1, MEN2, neurofibromatosis type 1, Cowden syndrome, Peutz-Jeghers syndrome, familial adenomatous polyposis). A separate group are additionally genetically determined syndromes/disorders in which there is a risk of cancer development, such as: Fanconi aneamia, *Xeroderma pigmentosum*, Ataxia-teleangiectasia, Nijmegen syndrome, which are inherited in an autosomal recessive manner. Diagnosis of these syndromes/disorders is based on assessment of clinical features and genetic testing.

Pre-test and post-test genetic consultations

An ideal setting for oncogenetic counselling includes pre-test and post-test genetic consultations. The initial visit to a genetic clinic concentrates on collecting the family history and pedigree construction, as well as taking a personal medical history [8, 19].

Medical information should be gathered on family members from at least three generations. It includes details of any malignant and benign tumours and other features such as consanguinity. The evaluation of clinical and pedigree data not only serves the purpose of diagnosing an alleged cancer predisposition syndrome, but also the selection of individuals eligible for genetic testing [8, 12, 16, 17].

Suspicion/recognition of hereditary cancer predisposition

Families with the same or related types of cancer affecting numerous family members, early onset of cancers (usually younger than in sporadic forms of cancer, often younger than the age of 50) and atypical or rare cancers (for example, male breast cancer), multifocal cancers or multiple cancers in one person comprise red flags for cancer predisposition syndromes.

A meticulous analysis of family history serves the purpose of identifying cancer patterns that fulfil criteria for recognition of cancer predisposition syndromes. Especially in situations of

three affected relatives with the same related cancer across a minimum of two generations and at least one patient under 50 years of age [8, 9, 20].

However, due to the high overall frequency of cancers, not all individuals with cancer from a family with a hereditary predisposition will carry a causative mutation. For example: larynx cancer in a lifelong cigarette smoker should not be assumed to be caused by a familial *BRCA1* mutation. Furthermore, in family with a *BRCA1* mutation, there might be relatives without a *BRCA1* mutation who develop breast or ovarian cancer. This phenomenon is called "phenocopy". It means that independent, different environmental or genetic factors are responsible for the same type of cancer.

In some instances the structure of the family itself (a small number of relatives or early deaths, no information on relatives, adoption or assisted reproduction, etc.) limits pedigree assessment. Negative family history might be also the result of false data, incomplete penetrance (not all people with a genetic change will develop cancer) or sex-related penetrance, for example, inheriting through a male line a genetic variant consistent with ovarian cancer. Those factors are: atypically young age of cancer onset, multiple tumours in one individual, rare types of cancers or tumour properties (ex. triple negative breast cancer or microsatellite instability in colorectal cancer) may indicate a genetic background without specifically meeting the diagnostic criteria for a syndrome. For example, early onset female breast cancer (before age 31 years) or adrenocortical carcinoma or choroid plexus tumour irrespective of family history might be indicative of Li-Fraumeni syndrome [21].

Personal history may prove relevant to making the correct diagnosis. The presence of hamartomatous gastrointestinal polyps would require a differential diagnosis between Peutz-Jeghers syndrome, juvenile polyposis syndrome and Cowden syndrome in the least. A history of multinodular goitre and uterine fibroids may prompt a careful dermatological examination of a patient for pathognomonic signs of Cowden syndrome [7, 15].

Genetic tests

Assessment of family and personal histories forms the basis for formulating indications for genetic testing. There are several approaches that depend not only on the clinical findings but also on other factors such as the resources available for testing. Molecular genetic testing may include:

- direct mutation diagnosis,
- single gene sequencing,
- multigene panels.

Direct mutation analysis is required when a pathogenic variant has previously been found in a relative. In cases when it is clinically possible to determine a diagnosis or at least have a high probability of making one, single gene testing might be considered. In instances when the condition might be related to mutations in many different genes, multigene panels have been introduced. There are no uniform recommendations on the number of genes that should be included in such a panel, and there are ongoing discussions on the relevance of particular genes to some cancers [18, 22, 23].

Discussion on genetic testing

The pre-test consultation should include a comprehensible evaluation of the advantages and disadvantages of molecular genetic testing for the patient and the possible outcomes of the testing (positive result, negative result, inconclusive result and accidental findings), as well as the consequences of diagnosing cancer predisposition syndrome for other family members. Acknowledging the magnitude of risk of developing cancer caused by the identified mutation, gives the individual opportunities for managing that risk by making life style changes, undergoing regular screening or having preventive surgical treatment. For many individuals it relieves the anxiety connected to the uncertainty of not knowing the risk. However, there are limitations to genetic testing that necessitate consideration. Receiving a negative result will never alleviate the risk of developing cancer – most of the cases are caused by acquired somatic mutations.

It is also important to remember that there are no indications for genetic testing in a relative of an individual with cancer and a negative genetic test result. However, in some cases a different test might be offered, but this depends on additional circumstances and might be prompted by acquiring more clinical and family history information.

When the clinical criteria of a cancer predisposition syndrome are fulfilled, but no genetic alteration can be found, counselling about the management of cancer risk should be provided to individuals elected on the basis of a pedigree.

Sometimes the results might be inconclusive, not providing an accurate answer to the question of the exact level of risk. Those genetic alterations are known as variants of unknown significance. In some rare instances, performing a genotype-phenotype correlation in family members might elucidate the significance of a change that has been found.

For some individuals, a positive result may cause permanent anxiety of a diagnosis that seems all but inevitable. Each of the above-mentioned issues should be brought to the individual's attention and hence they formulate the underpinnings of informed consent. Signing a consent form should be preceded by disclosing full information on the possibilities and limitations of a given genetic test, the consequences of diagnosing a cancer predisposition syndrome and its management [8, 16, 17, 22, 23].

Consultations after genetic test

The post-test consultation includes the explanation of the result of the genetic testing to the individual and his family and the various possibilities of cancer risk management that are open to the individual. Depending on the gene involved, a positive result (pathogenic or likely pathogenic variant) may convey different levels of risk of cancer development in dif-

ferent organs. For example, particular mutations in *TP53* have been linked to different levels of risk of different types of cancer (https://tp53.isb-cgc.org/). Each significant change (pathogenic or potentially pathogenic) will be related to a specific clinical course of action in the field of prophylaxis and the treatment of the patient. This is reflected in various clinical recommendations [9, 15, 24].

A positive result is also a proof of hereditary cancer predisposition syndrome, hence it is important to relatives at risk of harbouring the mutation. With which relatives to disclose the information should be discussed. If the result of the genetic testing is negative – it must be interpreted in the context of the information gathered during previous consultations. A negative result might not exclude a cancer predisposition syndrome. One of the most difficult issues are inconclusive results. With the introduction of next generation sequencing, variants of unknown significance (VUS) have become a considerable problem, requiring great caution when attempting interpretation. It is important to attempt reanalysis of VUS as their interpretation might change as more evidence becomes available.

It is important to remember that the risk of cancer development is never zero. Each individual, even in a situation of exclusion of a cancer predisposition syndrome, has a population risk of cancer development. Individuals, according to their genetic makeup, have different levels of cancer risk development. Life style changes, screening strategies and, in some cases, prophylactic surgical interventions, according to the level of cancer risk development should be discussed.

Conclusion

Cancer predisposition syndromes are rare in oncological practise. However, their recognition has a significant impact on screening and the management of individuals with a high risk of cancer development. Adequate care for these patients can be provided only in a multidisciplinary setting that includes an oncologist and clinical geneticist.

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Agnieszka Stembalska
Wroclaw Medical University
Department of Genetics
ul. K. Marcinkowskiego 1
50-368 Wrocław, Poland
e-mail: agnieszka.stembalska@umw.edu.pl

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