I. GENETICS

ELEMENTS OF RISK ASSESSMENT AND GENETIC COUNSELING IN CANCER

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Abstract
People who have been diagnosed with cancer at an atypically young age, which have a rare cancer, childhood adrenal carcinoma, right-sided colon cancer, multiple primary cancers, cancers associated with birth defects and people with a strong family history of cancer are usually considered to be candidates for genetic counseling.
Key words: cancer, genetic counseling

Introduction

People are usually considered to be candidates for genetic counseling if they have a strong family history of cancer. In general, this means a family history that includes several affected relatives, with at least some affected at atypically early ages. The definition of a strong family history, however, varies for different cancers.

People who have been diagnosed with cancer at an atypically young age; have a rare cancer, e.g., childhood adrenal carcinoma; unusual presentation, e.g., right-sided colon cancer; multiple primary cancers; cancers associated with birth defects; or, in some cases, have extreme cancer anxiety, even in the absence of risk, may also be candidates for genetic counseling.

Individuals who are candidates for genetic testing receive genetic counseling prior to undergoing testing to facilitate decision making. This gives them time to fully understand both the various medical uncertainties and psychosocial risks and benefits of this information (1).

Certain components are common to the genetic counseling process, including those focused on cancer risk. These include medical, genetic and counseling components such as constructing and evaluating a pedigree; eliciting and evaluating personal and family medical history and providing information about genetic risk. When testing is needed, genetic counseling incorporates pretest counseling, testing, post-test counseling, and follow-up. This may include discussing, ordering and interpreting clinical genetic laboratory tests. Much preparation time outside the appointment is spent obtaining and reviewing medical records, seeking information about diagnoses in the differential diagnosis list, finding support groups and patient resources, communicating with other specialists, and case documentation.

In some instances, physical findings may be important in determining whether or not a cancer syndrome is present; this requires a targeted physical examination by a medical professional for physical findings specific to a genetic syndrome.

Cancer Risk Counseling

Genetic counseling has been defined as "a communication process which deals with the human problems associated with the occurrence, or risk of occurrence, of a genetic disorder in a family". The process involves an attempt by one or more appropriately trained persons to help the individual or family to:

1. comprehend the medical facts including the diagnosis, probable course of the disorder, and the available management;
2. appreciate the way that heredity contributes to the disorder, and to the risk of recurrence (occurrence), in specific relatives;
3. understand the alternatives for dealing with the risk of recurrence (occurrence);
4. choose a course of action which seems to them appropriate in view of their risk, their family goals, and their ethical and religious standards and act in accordance with that decision; and
5. make the best possible adjustment to the disorder in an affected family member and/or to the risk of recurrence (occurrence) of that disorder.

Central to genetic counseling philosophy and practice are the principles of voluntary utilization of services, informed decision making, attention to psychosocial and affective dimensions of coping with genetic risk, and protection of patient confidentiality and privacy (2).

An important objective of genetic counseling is to provide an opportunity for shared decision making when the medical benefits of one course of action are not demonstrably superior to another.

The relationship between availability of effective medical treatment for mutation carriers and clinical validity of a given test affects the degree to which personal choice or physician recommendation is supported in counseling at-risk individuals. Genetic counseling generally involves some combination of rapport-building and information gathering; establishing or verifying diagnoses; risk assessment and calculation of quantitative occurrence/recurrence risks; education and informed consent processes; psychosocial assessment, support and

counseling appropriate to a family's culture and ethnicity; and other relevant background variables.

In the past decade, genetic counseling has expanded to include discussion of genetic testing for cancer risk as more genes associated with inherited cancer susceptibility have been discovered. Cancer genetic counseling often involves a multidisciplinary team, which may include a genetic counselor, genetic advanced practice nurse, or medical geneticist, mental health professional, and medical expert such as an oncologist, surgeon, or internist. The process of counseling may require a number of visits in order to address the medical, genetic testing, and psychosocial support issues. Even when cancer risk counseling is initiated by an individual, inherited cancer risk has implications for the entire family.

Because genetic risk affects biological relatives, contact with these relatives is often essential to collect an accurate family and medical history. Cancer genetic counseling may involve several family members, some of whom may have had cancer, and others who have not.

Certain features of genetic disease susceptibility highlight the importance of genetic counseling. Specifically, an accurate assessment depends on detailed family history and, conversely, information about one individual has implications for others in the family. The purpose of risk counseling is to provide information about an individual's empiric risk of cancer.

If the assessment indicates an increased cancer risk, counseling may include discussion of cancer risk management strategies or of options for genetic testing (3). Risk counseling may also lead to reassurance if cancer risk is found not to be greater than the average, or substantially less than the person had anticipated. In some cases, the purpose of counseling includes helping the individual to explore feelings about his/her personal risk status and to make a healthy adjustment to that risk status. Either alone, or in consultation with a mental health provider, professionals offering cancer genetic counseling attempt to assess whether the individual's expectations of counseling are realistic and whether there are factors suggesting unusual risk of adverse psychological outcomes following disclosure of risk and/or genetic status. Sometimes, referral for psychotherapeutic treatment prior to or in lieu of testing may be recommended.

There have been some studies of patient satisfaction with cancer genetic counseling services. For example, one survey of participants after the first year of operation of a cancer genetics program reported that the clinical services met the needs and expectations of most people.

Patients reported that the best parts of the experience were having personalized summary letters and family pedigrees, learning that cancer risk was either lower than expected, or realizing that one had been justified in suspecting the inheritance of cancer in one's family, allowing for cleansing of one's conscience of burdensome guilty feelings, as well as simply having a chance to talk to someone about cancer concerns (4).

Follow-up is often multidisciplinary, with input from, and referral to, professionals trained in genetic counseling, nursing, social work, psychology, preventive medicine, public health, occupational health, and mental health, and as needed to other medical specialties such as surgery, gastroenterology, gynecology, or oncology. Because inherited cancers affect more than the individual, the entire family may become involved.

Taking a Family History

It is essential to summarize family history information in the form of a pedigree. A pedigree, or family tree, is a standardized graphic representation of family relationships, in which patterns of disease transmission are tracked. A graphic illustration facilitates identification of patterns of transmission, recognition of specific hereditary cancer syndromes, and assists in determining the best methods for risk assessment.

Factors suggesting inherited cancer risk include the following:

•Clustering of the same type of cancer in close relatives.

•Unusually early age of cancer onset.

•Two or more primary cancers in a single relative.

•Evidence of autosomal dominant inheritance.

•Bilaterality in paired organs.

•Patterns of cancer in the family that are associated with a known cancer syndrome.

A cancer family history typically includes the following:

•Both maternal and paternal relatives. Hereditary cancer syndromes can be inherited from either the mother or the father.

•Notation of nonpaternity, consanguinity, and use of assisted reproductive technology (e.g., donor egg or sperm).

•Race, ancestry and ethnicity information for all grandparents. This may influence decisions about genetic testing, because specific mutations may occur with increased frequency in selected populations.

•Seemingly unrelated conditions such as birth defects or other nonmalignant conditions of children and adults as they may aid in the diagnosis of a cancer susceptibility syndrome.

•A minimum of 3 generations. This will help identify inheritance patterns since cancer is often an adult-onset disease.

For any relative with cancer, collect the following information:

•Type of each primary cancer.

•Age of diagnosis for each primary cancer.

•Where the relative was diagnosed and/or treated.

•If the individual is still living, current age; if deceased, age at death and cause of death.

•Carcinogenic exposures (e.g., tobacco use, radiation exposure).

•Other significant health problems.

For any relative not affected with cancer, collect the following information:

•Current age or age at death.

•If deceased, cause of death.

•Any surgeries that reduce the risk for cancer.

•Whether routinely screened for cancer.

•Any nonmalignant features of the syndrome in question.

•Carcinogenic exposures.

•Other significant health problems.

People often have incomplete or inaccurate information about the cancer history in their family (e.g., because of adoption, loss of contact with relatives, small family size, or deaths at an early age from unrelated conditions).

Family histories change over time; therefore, it is useful to update pedigrees periodically. Self-reported family history may contain errors. Verification of medical diagnoses through medical records, tumor registries, or death certificates may improve the risk assessment.

Analysis of the Family History

Since a family history of cancer is one of the important predictors of cancer risk, analysis of the pedigree constitutes one important aspect of risk assessment.

The index of suspicion should be raised by:

•Multiple cancers in close relatives, particularly in multiple generations.

•Early age of onset, before 40 to 50 years for adult onset cancers.

•Multiple cancers in a single individual.

•Bilateral cancer in paired organs (e.g., breast, kidney).

•Recognition of the known association between etiologically related cancers in the family.

•Presence of congenital anomalies or precursor lesions that are known to be associated with increased cancer risk (e.g., presence of atypical nevi and risk of malignant melanoma).

•Recognizable Mendelian inheritance pattern.

There are hundreds of inherited conditions associated with an increased risk of cancer. Diagnostic criteria for different hereditary syndromes incorporate different features depending on the original purpose of those defining the syndrome, e.g., for gene mapping, genotype-phenotype studies, epidemiological investigations, population screening, or clinical service.

Thus, a syndrome such as hereditary nonpolyposis colorectal cancer (HNPCC) can be defined for research purposes by the Amsterdam Criteria as having 3 individuals with colorectal cancer, 2 generations, of which 1 person is less than 50 years of age, better known as the 3-2-1 rule. These criteria have limitations in the clinical setting, however, in that they ignore endometrial and other extracolonic tumors known to be important features of HNPCC.

Risk Perception

A person's subjective view of risk may differ from his/her estimated statistical risk. The individual's perception of their cancer risk, however, may be the most important factor in determining decisions about screening or other risk reduction strategies.

Thus, it is important to begin a risk assessment process by eliciting the person's perception of their risk as well as how concerned they are about the risk and how this has affected their day to day life.

The Option of Genetic Testing

Factors to take into consideration in offering testing

1. Pedigree suggesting an inherited cancer syndrome.

Experts recommend offering genetic testing only when a pedigree analysis suggests the presence of an inherited cancer syndrome for which specific mutations have been identified. American Society of Clinical Oncology (ASCO) guidelines propose that genetic testing should be offered when:

•An individual has a personal or family history suggestive of a genetic cancer susceptibility syndrome.

•The results of the test can be interpreted.

•Testing will influence medical management.

2. Value of testing an affected family member first.

Genetic susceptibility testing generally yields the most useful information when a living family member affected with the cancer of concern is tested first to determine if a genetic basis for the cancer in the family can be established. If a mutation previously associated with cancer risk is demonstrated in the affected family member, other family members may be tested for the presence or absence of this specific mutation. If no mutation is found in an affected family member, testing is considered uninformative regarding the possible inherited basis for cancer in that family, and thus there is no basis for testing unaffected relatives (5, 6).

Where there is no close, living, affected relative, other options may be discussed with the patient and the testing laboratory. These generally involve weighing a decision to test stored tissue on a deceased relative or to test an unaffected person without prior testing of an affected family member. Tests done on stored tissue are technically difficult and may not yield a definitive result. Testing an unaffected person without prior testing of an affected relative often is uninformative, because a negative test does not rule out the presence of a cancer susceptibility gene in the family or the subject. In addition, counseling needs to take into account the risk and consequences of a false positive test.

Determining the test to be used

Genetic testing is highly specialized. Any given test is usually performed in only a small number of laboratories. There are also multiple molecular testing methods available, each with its own costs, strengths, and weaknesses. Depending on the method employed and the extent of the analysis, different tests for the same gene will have varying levels of sensitivity and specificity. Even

assuming high analytic validity, genetic heterogeneity makes test selection challenging.

A number of different genetic syndromes may underlie the development of a particular cancer type. Thus, hereditary colon cancer may be due to having HNPCC, Peutz-Jegher syndrome (PJS), juvenile polyposis syndrome (JPS), or other syndromes. Each of these has a different genetic basis. In addition, different genes may be responsible for the same condition, e.g., HNPCC can be due to mutations in 1 of at least 6 mismatch repair genes. There is also allelic heterogeneity, i.e., different mutations within the same gene can confer different risks or be associated with a different phenotype.

Thus, selection of the appropriate genetic test for a given individual requires considerable knowledge of genetic diagnostic methods, correlation between clinical and molecular findings and access to information about rapidly changing testing options.

All individuals considering genetic testing should be informed that they have several options even after the genetic testing has been completed. They may decide to receive the results at the post-test meeting, decide to delay result notification, or decide not to receive the results of testing (7).

Importance of Pretest Counseling

The complexity of genetic testing for cancer susceptibility has led experts to suggest that careful, in-depth counseling should precede any decision about the use of testing in keeping with the accepted principles for the use of genetic testing. The clinician who opts to take on this responsibility must provide the depth of content and time required to ensure that the patient can make an informed testing choice.

Qualitative and quantitative research studies indicate that families hold a variety of beliefs about the inheritance of characteristics within families; some of these beliefs are congruent with current scientific understanding while others are not. These beliefs may be influenced by education, personal and family experiences, and cultural background. Since behavior is likely to be influenced by these beliefs, the usefulness of genetic information may depend on recognizing and addressing the individual's pre-existing cognitions. This process begins with initial discussion and continues throughout the genetic counseling process.

Psychological Impact of Genetic Information/Test Results on the Individual

An accurate assessment of psychosocial functioning, and of emotional factors related to testing motivation and potential impact and utilization, is an important part of pretest counseling. Generally, a provider inquires about a person's emotional response to the family history of cancer and also about a person's response to his/her own risk of developing cancer. People have various coping strategies for dealing with stressful circumstances such as genetic risk. Identifying these strategies and ascertaining how well or poorly they work will have implications for the support necessary during post-test counseling, and will help personalize the discussion of anticipated risks and benefits of testing.

Taking a brief history of past and current psychiatric symptoms (depression, extreme anxiety, suicidality) will allow for an assessment of whether or not this individual is at particular risk of adverse effects following disclosure of results. In such cases, further psychological assessment may be indicated.

In addition, cognitive deficits in the person may significantly limit understanding of the genetic information provided and hinder the ability to give informed consent, and may also require further psychological assessment. Emotional responses to cancer risk may also affect overall mood and functioning in other areas of life such as home or work. Education and genetic counseling sessions provide an opportunity for ongoing informal assessment of the affective as well as cognitive aspects of the health communication process. Since behavioral factors influence adherence to screening and surveillance recommendations, consideration of emotional barriers is important in helping a person to choose prevention strategies as well as in discussing the potential utility of genetic testing.

Psychological Impact of Genetic Information/Test Results on the Family

In addition to making an assessment of the family history of cancer, the family as a social system may also be assessed as part of the process of cancer genetic counseling. Hereditary susceptibility to cancer may affect social interactions and attitudes toward the family.

The practitioner may use the above framework to guide inquiries about the relationship of the individual to 1) the affected members of the family, or 2) others who are considering or deciding against the consideration of genetic counseling or testing. Inquiries about how the family shares (or does not share) information about health, illness, and genetic susceptibility may establish whether the individual feels under pressure from other family members or anticipates difficulty in sharing genetic information obtained from counseling or testing.

Inquiries about the present health (new diagnoses or deaths from cancer) or relationship status (divorce, marriage, grieving) of family members may inform the provider about the timing of the individual's participation in counseling or testing and may also reveal possible contraindications for testing at present.

Many individuals benefit from follow-up counseling and consultation with medical specialists after disclosure of test results to allow an opportunity for further discussion of their feelings about their risk status, their options for risk management to incorporate screening and detection procedures, and implications of the test result for other family members.

References

1. ASHG statement. Professional disclosure of familial genetic information. The American Society of Human Genetics Social Issues Subcommittee on Familial Disclosure. Am J Hum Genet 62 (2): 474-83, 1998. [PUBMED Abstract]

2. Biesecker BB: Goals of genetic counseling. Clin Genet 60 (5): 323-30, 2001. [PUBMED Abstract]

3. Petersen GM: Genetic testing. Hematol Oncol Clin North Am 14 (4): 939-52, 2000. [PUBMED Abstract]

4. Stadler MP, Mulvihill JJ: Cancer risk assessment and genetic counseling in an academic medical center: consultands satisfaction, knowledge, and behaviour in the first year. J Genet Couns 7 (3): 279-297, 1998

5. Green MJ, Biesecker BB, McInerney AM, et al.: An interactive computer program can effectively educate patients about genetic testing for breast cancer susceptibility. Am J Med Genet 103 (1): 16-23, 2001. [PUBMED Abstract]

6. Green MJ, McInerney AM, Biesecker BB, et al.: Education about genetic testing for breast cancer susceptibility: patient preferences for a computer program or genetic counselor. Am J Med Genet 103 (1): 24-31, 2001. [PUBMED Abstract]

7. Burke W, Pinsky LE, Press NA: Categorizing genetic tests to identify their ethical, legal, and social implications. Am J Med Genet 106 (3): 233-40, 2001 Fall. [PUBMED Abstract