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Genetic Cancer Syndromes

From the Editor and Authors:

The spring 1999 *Genetic Drift* provides a review of current information on familial cancers which primary care providers are likely to encounter in the course of medical practice. The first two articles discuss the two most common and well understood familial cancer syndromes, breast/ovarian and colon, recognizing that familial cases still account for only a few percent of total cancers of these types. A number of other cancers that occur within families are summarized in the third article. While it is estimated that about 15% of cancer is due to inherited cancer-predisposing genes, the identification of individuals with an increased cancer risk is of paramount importance. The recognition of at-risk families provides a rare opportunity for health care professionals to recommend a cancer surveillance program and also to provide genetic counseling for other family members. A common theme in all three articles is the importance of accurately documenting a three-generation family history; we encourage all providers to inquire about family history of cancer. Useful web sites, hereditary cancer genetics services available in our region, and information about cancer research opportunities for families are listed at the conclusion of this issue.

This issue was spearheaded by Vickie L. Venne, MS (UT), with contributions from Amy Cronister, MS (AZ), Mark H. Greene, MD (AZ), Lisa Mullineaux, MS (CO), and Catherine Klein, MD (CO).

Carol L. Clericuzio, MD (NM), Editor

Genetics of Breast Cancer: A Review for Primary Care Providers

Introduction

In the United States, breast cancer is the most frequently occurring cancer among women, with a lifetime risk of 1 in 8. Studies suggest that approximately 9% of all breast cancer in the United States is accounted for by a positive family history of breast cancer[1]. Familial clustering of breast cancer may be a coincidence, or it may be due to an underlying genetic risk inherited in a polygenic, multifactorial or single gene pattern. Hereditary breast cancer is real and may produce dramatic familial aggregations of breast cancer. At least eight identified genes have been associated with inherited breast cancer susceptibility (summarized by Greene[2]). Others are likely to be found. BRCA1 and BRCA2 are currently the most important of these but account for less than 5% of all breast cancers.

Many women with a family history of breast cancer are concerned about their own risk of developing cancer and medical management options that might reduce this risk. They will turn to their family physicians for accurate information. In response, primary care physicians must be familiar with cancer risk assessment, hereditary syndromes, the usefulness of predictive genetic testing and referral mechanisms to make appropriate patient management decisions.

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Family history taking and cancer risk assessment

Multiple epidemiological studies have documented that a *reported* history of breast cancer among relatives is a reproducible predictor of breast cancer risk. Data suggest that, for the vast majority of women with a positive family history of breast cancer (1 or 2 affected relatives), the relative risk for breast cancer is increased 2-3 fold[3]. The risk escalates dramatically, however, for families with premenopausal breast cancer, bilateral disease and multiple affected family members.

Identifying women with a positive family history is an important first step to providing accurate cancer risk assessment. It is vital to gather information regarding both the maternal and paternal side of the family. For each family member with cancer the following information should be documented:

- the site of origin of all reported primary cancers
- whether the tumor was bi- or unilateral in paired organs
- age at diagnosis
- lineage (either maternal or paternal) and degree of relationship

When reviewing the completed family history, families can be assigned to lower or higher risk categories. Lower risk families typically present with fewer than three cases of breast cancer, absence of ovarian cancer and an older age of breast cancer onset (greater than 50 years old). An hereditary syndrome (or higher risk family) should be suspected if the following are noted:

- a history of breast or ovarian cancer in two or more first degree relatives in either paternal or maternal lineage
- early age of onset (<50)
- bilateral or multifocal breast cancer
- specific constellation of tumors that comprise a known breast cancer syndrome, e.g.
  - breast, ovarian, prostate and colon (hereditary breast cancer)
  - breast, brain, adrenocortical tumors, sarcoma, leukemia (Li Fraumeni syndrome)
  - breast, lymphoma, and pancreatic cancer (ataxia telangiectasia)
  - breast, thyroid and skin (Cowden syndrome)
- absence of environmental influences

Lower risk families

The primary care provider may help allay the inappropriate fears expressed by many patients simply by (a) pointing out the relative rarity of truly hereditary breast cancer, (b) reminding patients that "familial" and "hereditary" are not the same, and (c) providing a description of the features of hereditary breast cancer (which only applies to a small minority of patients with a family history of breast cancer). Even in the absence of clear proof of efficacy, a common-sense set of recommendations for "good breast health" can also be offered, and includes:

- maintaining ideal body weight
- participating in regular aerobic exercise
- consuming a diet that emphasizes fresh fruits, vegetables, chicken and fish, and de-emphasizes beef
- moderating alcohol consumption
- minimizing radiation exposure to the breasts (particularly in teenagers)
- thoughtful deliberation over decisions regarding use of oral contraceptives, estrogen replacement therapy and the appropriateness of tamoxifen. (Results from the Breast Cancer Prevention Trial suggest that tamoxifen may have an important role to play in reducing breast cancer incidence in carefully selected, appropriately informed women at increased risk of breast cancer[4].)

For some patients, fears do not subside until additional information is given. Providing patient-specific cancer risk assessment to these individuals may prove beneficial. A comprehensive evaluation may be indicated, especially for women who have had an abnormal mammogram or biopsy indicating a precancerous lesion. This may best be completed by a multidisciplinary team which can assess cancer risk, review cancer risk factors and make recommendations about appropriate prevention and screening.

Among unaffected relatives from lower risk families, cancer risk assessment is not standardized. In addition to family history, a personal health history as well as occasional laboratory and radiographic studies must be considered and interpreted. Sophisticated mathematical models can be employed to estimate risk of developing breast cancer for unaffected relatives in families in which there is not a significant history of cancer in extended members. One such model, published by Claus et al.[5], predicts the cumulative risk of breast cancer at specific ages. Presented in detailed tables, this model takes into account the age of onset for affected relatives and the age of the patient. It does not account for other breast cancer risk factors. Another model, published by Gail et al.[6], does incorporate breast cancer risk factors including age at menarche and number of previous breast biopsies into its mathematical formula. Although valuable in predicting risk in women undergoing annual mammography, this model is limited by considering only first degree relatives and not accounting for age of diagnosis of breast cancer.

Higher risk families

To obtain the most up-to-date information about the role that susceptibility genes play in the development of cancer and to accurately assess cancer genetic risk, high risk families should be referred to a program which specializes in managing hereditary cancer. These clinics include education and counseling about cancer risk, cancer risk reduction, and effective screening and prevention options. Genetic counseling is essential to ensure that patients understand the information presented, appreciate potential medical and psychological implications of hereditary cancer and have an opportunity to explore the limitations and benefits of available testing options.

BRCA1 and BRCA2

Overall, 52% of breast cancer families with at least four cases of breast cancer are linked to BRCA[1]. Cumulative breast cancer risk among gene carriers is approximately 80% by age 70. This figure may be high due to an ascertainment bias of particular populations or of high risk families. The risk of developing cancer may be lower in women with less dramatic family histories or in women whose mutations are identified via population screening[7,8]. Among BRCA1 mutation carriers with a first breast cancer, the risk of contralateral breast cancer may be as high as 65% by age 70. The risk of ovarian cancer in these same women has been estimated between 30-65% by age 70[7,9,10]. Colon cancer is estimated to occur four times more frequently among BRCA1 mutation carriers than expected from general population rates: the absolute risk is 6% by age 70 (1-2% in non-carriers). Prostate cancer may occur 3.3 times more often than expected in male BRCA1 mutation carriers, with an absolute risk of 8% by age 70[9].

The prospect that the cloning of BRCA1 would quickly lead to a simple genetic test has been thwarted by the gene's large size and the enormous number of distinct, disease-related mutations which have been identified to date. Over 200 BRCA1 mutations have been documented, some of which seem specific to particular populations. Appropriate testing for the first member of most families in which mutation status is unknown is to offer full gene sequencing.

Of those families which have an inherited predisposition to developing breast cancer, about 35% appear to be linked to a second breast cancer susceptibility gene, BRCA2[11]. Male breast cancer seems to be part of the BRCA2 tumor spectrum (although it is observed in occasional BRCA1 families as well) and is estimated to occur in approximately 6% of mutation carriers[11]. Lifetime risk of breast cancer in women with BRCA2 mutations is similar to those with BRCA1. In contrast, the cumulative lifetime risk of ovarian cancer, while still higher than that in the general population, appears to be 10-20% lower than that of women who have a BRCA1 mutation[7,11,12]. Like BRCA1, multiple distinct mutations in BRCA2 have been identified, scattered rather evenly throughout this large gene.

It has been long appreciated from breast cancer case-control studies that Jewish women are at mildly increased risk of breast cancer compared to non-Jewish women. One of the more intriguing observations regarding BRCA1 and BRCA2 has been the recognition that three specific mutations (185delAG, 5382insC and 6174delT) occur with a very high frequency (>2%) among persons of Ashkenazi Jewish extraction. These three mutations have been reported in approximately 25% of site specific breast cancer families and up to 90% of breast and ovarian cancer families[13]. In light of these data, women of Ashkenazi Jewish ancestry who have at least one first degree relative with premenopausal breast cancer or ovarian cancer are appropriately referred to a high risk breast cancer clinic.

Predictive testing for BRCA1 and BRCA2

The issue as to when to offer predictive genetic testing for BRCA1 and BRCA2 is proving remarkably contentious. None of the cancer susceptibility tests currently available appears to be appropriate for screening asymptomatic individuals in the general population, although the population-specific mutations described among Ashkenazi Jews may reach that status in the future. The evaluation of individuals from high risk families with well defined syndromes is far less clear. Most academic, professional and government organizations that have addressed this issue have concluded that it is premature to offer BRCA1 and BRCA2 testing as a routine clinical service. The American Society of Clinical Oncology (ASCO) has published a position paper on this subject[14]. This statement and the companion comments provide an excellent summary of the issues:

The basic elements of informed consent for germline DNA testing are complex and extensive. Patients must be given: (1) information on the specific test being done; (2) implications of a positive and negative test; (3) possibility that the test will not be informative; (4) options for risk evaluation without genetic testing; (5) risk of passing a mutation to children; (6) technical accuracy of the test; (7) fees involved in testing and counseling (up to $2500); (8) risk of psychological distress; (9) risk of employment and insurance discrimination; (10) need for confidentiality; and (11) options and limitations of medical surveillance and screening after testing.

The Breast Cancer Linkage Consortium data base and mathematical models developed by Shattuck-Eidens et al.[15], Parmigiani et al.[16], Couch et al.[17] and Frank et al.[18] can be used to compute estimated probabilities that a BRCA1 and BRCA2 mutation will be found in women of various ages, cancers and relationship combinations. When included in the discussion of predictive gene testing, this information may enhance informed decision making regarding BRCA1 and BRCA2 testing.

What benefits might accrue to those who undergo predictive genetic testing? In the context of testing members of a family *known* to carry a BRCA1 or BRCA2 mutation, most persons tested will achieve knowledge of their gene status, thereby, eliminating pre-test ambiguity. *In that setting*, for those who do not have the mutation seen in other members of their family, additional potential benefits include:

- relief from fear of genetic cancer risk, both for themselves *and their children*
- elimination of the need to consider prophylactic breast and/or ovarian surgery
- the ability to make choices regarding exogenous hormone use without concern about genetic interactions
- general improvement in their sense of well-being

For those who test positive, one might anticipate:

- more accurate quantification of cancer risks
- less uncertainty about the potential benefits of prophylactic surgery
- the ability to elect more intensive, site-specific cancer surveillance

- enhanced motivation to make prudent lifestyle change which *might* reduce cancer risk.

Operating counter to this cautious approach to the introduction of predictive testing are the commercial interests that hold the patents on the tests to be marketed and that stand to profit enormously if the tests are widely used. Several commercial laboratories currently market BRCA1 and BRCA2 testing. They are, to their credit, making an effort to ensure that testing is being done as part of a comprehensive genetic testing/counseling program, but the ultimate responsibility will rest with busy clinicians who are relatively ill-equipped to present the subtleties and complexities of cancer genetic risk assessment and predictive genetic testing. It is important to remember that commercial availability of a genetic test does *not* automatically mean it is suitable for routine general use.

Based on the data presented, guidelines for referring a patient to discuss predictive genetic testing include:

- a woman with breast cancer diagnosed younger than age 30
- a woman with breast or ovarian cancer diagnosed younger than age 50 who has a sister, mother, or daughter with breast or ovarian cancer diagnosed younger than age 50
- an affected woman from a family with two or more breast cancers *and* one or more ovarian cancers
- an unaffected first-degree relative of someone with a known mutation in BRCA1 or BRCA2
- an Ashkenazi Jewish woman with breast cancer diagnosed at less than age 40 or ovarian cancer diagnosed at any age.

Ideally, in a family which has not previously been shown to have a disease-related mutation, genetic testing should start with a family member who has had cancer.

Summary

While the process of cancer risk assessment and predictive genetic testing is complex, much of the basic information regarding the clinical characteristics of hereditary breast cancer, the relative rarity of BRCA1 and 2 mutations, and sensible recommendations for breast health can be managed by primary care providers. Currently, predictive genetic testing is best done through specialty referral. We are at the beginning of an exciting period in genetic oncology, but much remains to be learned. To the greatest extent possible, genetic testing for cancer susceptibility should be made available to selected patients as part of preventive oncologic care only in conjunction with appropriate patient education, informed consent, support and genetic counseling. Patients may benefit greatly from accurate cancer risk assessment even when genetic testing is not undertaken.

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Genetics of Colorectal Cancer: A Review

Introduction

Colorectal cancer is the second leading cause of cancer deaths in the United States. An estimated 131,200 cases were diagnosed in 1997, representing about 9% of new cancer diagnoses. About 4-6% (or one in 25 to one in 17) of individuals in the United States will develop colorectal cancer, with approximate equal distribution between men and women. The average age of incidence is 67 years, with over 90% of deaths occurring in individuals over age 55. Incidence rates of colorectal cancer have declined in recent years, primarily as a result of increased screening and polyp removal, which inhibits progression of disease to invasive cancer.

Highly penetrant susceptibility syndromes inherited in an autosomal dominant pattern account for 3-7% of colon cancer cases. Another 15-20% show a less dramatic familial clustering, with the remainder considered 'sporadic' cancers. Although all colon cancers result from a series of somatic genetic mutations, those that are highly penetrant or familial are very likely the result of inherited mutations. The analysis of these mutations at the various stages of cancer or polyp development has allowed for a well-defined model for colorectal tumor development.

Occurrence of colorectal cancer in a first degree relative has been estimated to confer approximately a three-fold risk for this malignancy. At least one study demonstrated that the presence of adenomatous polyps in first degree relatives less than 60 years old also increases the risk three-fold. Although this information is useful for counseling, it presupposes knowledge of polyp information from the extended family members. In addition to genetic factors, pre-existing inflammatory bowel disease and a diet high in fat and low in fiber are recognized risk factors for colorectal cancer.

Obtaining a family history

Because the efficacy of early and regular screening for individuals at increased risk for developing colon cancer is well documented, it is important to identify high risk individuals. However, providing recommendations for medical management requires that a detailed and accurate medical/family history be obtained. Challenges to this task include the lack of knowledge many people have about health history of family members, especially concerning information from screening tests such as sigmoidoscopy or colonoscopy.

However, as outlined elsewhere in this newsletter, a complete family history includes identifying all the relatives (both maternal and paternal) from three generations with neoplasia. This usually comprises parents, siblings, children, grandparents, aunts, uncles, nieces, nephews and cousins. For each of these individuals, information about any primary cancer diagnosis is important (site, age of onset, stage). Information about colon screening (was it done, what were the results) is important to document. Many of these reported cancers and polyps will require medical record confirmation to assure that the most useful risk assessment is provided to the patient. Family and personal history of polyps is especially important to confirm due to the various types of polyps and their associated risks. Clues that the cancer may have an inherited component will include a young age of onset of cancers and several family members with polyps or colon cancer.

Common colon cancer syndromes

Familial colorectal cancers can be divided into two groups: those characterized by the presence of multiple benign colorectal polyps (polyposis); and those characterized by the absence of polyps. The two best understood diseases are familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC).

FAP is an autosomal dominant inherited disease due to mutations in the APC gene in chromosome 5. Affected individuals develop hundreds to thousands of adenomatous polyps during the second and third decades of life. These polyps resemble the sporadic adenomatous polyps that develop in the general population. Although an individual FAP polyp is no more likely to progress to cancer than is a sporadic polyp, their large numbers make it more likely that some will progress to cancer. The median age for colorectal cancer in patients with FAP is about 40. Thus, prophylactic colectomies are routinely performed on FAP patients to reduce their risk of developing cancer. Although one in 5000 individuals is affected with FAP in the United States, fewer than 1% of all colon cancer cases occur in patients with FAP, in part due to prophylactic colectomy. Patients with FAP are also at increased risk for cancers of the thyroid, small intestine, stomach and brain. FAP variants (e.g., Gardner syndrome) include extracolonic manifestations, such as soft tissue tumors, osteomas and dental abnormalities. Gardner syndrome, like FAP, is due to mutation of the APC gene. Approximately 25% of people with FAP represent individuals who have a new mutation, so not all patients with FAP have a family history of polyps or cancer.

HNPCC accounts for about 2 to 4% of colorectal cancers. The median age of disease onset is 40 years. These patients lack a marked increase in the number of precursor adenomas. Until recently, HNPCC kindreds had to be defined by pedigree analysis, with at least three first degree relatives in at least two different generations coupled with early onset colorectal cancer (less than 50 years old) in at least one affected family member. About 70% of families which meet this criteria have recognizable mutations. The majority of HNPCC patients inherit defects in the DNA mismatch repair genes, causing DNA to be genetically unstable and allowing rapid progression to cancer. Individuals who have inherited mutations in the HNPCC mismatch repair genes are at risk for cancers other than those of the colon. Other cancers seen in HNPCC families include those of the urinary tract, ovary, stomach and uterus.

Knowledge of mutation status in FAP and HNPCC families allows for presymptomatic diagnosis in members of those families. Individuals with that knowledge can increase surveillance or be reassured to a risk equal to that of the general population.

Less common colon cancer syndromes

In addition to FAP and HNPCC, there are a number of rarer syndromes with colon cancer. The identification of families,

genetic testing options, screening and medical management differ for each. Appropriate referrals to a cancer genetic center to clarify the syndrome for the patient, as well as his or her family, are important.

Turcot syndrome is an autosomal dominant condition in which the number of polyps ranges from 5-10 to over 100. In addition to colorectal cancers, brain tumors are also seen in individuals who have disease-causing mutations. Since the age of onset can be in the teens, screening recommendations include baseline flexible sigmoidoscopy from age 10. Because brain gliomas are seen at young ages, screening CT scans and MRIs are also recommended.

Peutz-Jeghers syndrome is also an autosomal dominant condition which involves polyps in the stomach, small bowel and colon. In addition to those sites, cancer can develop in the testes or ovaries. A characteristic feature of this condition is the melanin spots seen on the lips, buccal mucosa, face, forearms, and digits. The average age of diagnosis is the mid-20s and no known mutation has been identified in these families.

Muir-Torre syndrome is considered an HNPCC variant and includes sebaceous skin lesions that typically present in the fourth decade and a broad range of internal malignancies, such as stomach, endometrium, kidney, ovaries and bladder.

Familial juvenile polyposis, as the name indicates, involves juvenile polyps that can occur in the first decade of life. Most of the polyps are found in the colon, but some can be seen in the stomach and small bowel. About a third of the cases are familial, but the genetic and environmental factors involved are not yet known. The risk of cancer in these patients is 10-25% and screening recommendations are case specific.

Cowden disease is a rare condition that involves multiple hamartomatous polyps of the skin and mucous membranes. About one third of affected patients demonstrate polyps, although many are often not screened, since there does not appear to be an increased risk of developing colon cancer. It is an autosomal dominant condition, but penetrance is unclear because an asymptomatic skin papule is the most common manifestation and is often unrecognized. However, thyroid cancers have been seen and women are at an increased risk for breast cancer. Therefore, confirming the diagnosis and developing a screening regimen is important.

Familial colon cancers

The vast majority of colon cancer cases are considered sporadic, but many studies have demonstrated that first degree relatives of affected individuals have about a three-fold increased risk of developing colon cancer. In addition to sharing potentially inherited susceptibility mutations, these families often share similar environmental factors, such as geographical location and diet. Screening for first degree relatives of individuals with colorectal cancer should include an annual fecal occult blood analysis and sigmoidoscopy every three to five years. The age to begin screening is partially dependent upon the age of onset of the cancers in the family.

Predictive testing for colon cancer

The first step to offering predictive testing for colon cancer is to identify families that would likely have a mutation and develop a testing strategy for each family. The most appropriate person to be offered testing is a family member who has had cancer, often a member of the oldest generation. If a mutation exists in a family, it is more likely to be present in a person who has cancer. Testing the oldest generation first prevents a parent from learning about his or her genetic status as a result of information available from a child and honors the ability of the parent to make a voluntary, informed choice about personal testing. Once a mutation has been identified, the elements of informed consent for genetic testing (which are detailed in the breast cancer section of this document) should be met prior to obtaining blood on extended family members. These elements include a discussion of the risks, benefits and limitations, as well as the medical management options for people who have an identifiable mutation as well as those who do not. There are several key differences between predictive testing for colon cancer and breast cancer, including the efficacy of colon screening, which is higher than that for breast screening. In addition, since several of the colon cancer syndromes impact children, the rationale for testing minors in much stronger with regard to predictive testing for some colon cancer syndromes. Children who do not have the mutation seen in other family members benefit by not undergoing the invasive colon screening.

Summary

There are many recognizable inherited syndromes that involve colon cancer. Hence, it is valuable for the primary care provider to obtain a family history from individuals who are diagnosed with colon cancer. Clues that the cancer may have an inherited component include a young age of onset and other family members with polyps or colon cancer. For those families who meet appropriate criteria, referrals for genetic counseling and testing may help provide information about the cause of the cancer in the affected individual and allow for predictive testing for other family members. While assessment of risk for the extended family members and genetic testing can be complex (and best provided by cancer risk specialists), general information about colon cancer and screening should be offered by primary care providers.

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Other Types of Cancers and Tumors that Have an Inherited Risk

Introduction

It has long been recognized that many different benign and malignant tumors have an inherited risk. In recent years, several genes have been identified that predispose individuals to some of these tumors. In other cases, the approximate location of a gene has been identified, but the actual gene has not been found. In still others, a pattern of inheritance has been determined statistically, but the gene and its location have yet to be established. Inherited predisposition has been documented for many cancers, including breast, colorectal, other gastrointestinal cancers and tumors, colorectal adenomas, uterine, ovarian, prostate, pancreatic, lung, some endocrine tumors, renal cell carcinoma, some leukemias/lymphomas, testicular, brain tumors, retinoblastoma, sarcomas, thyroid and melanoma.

Documentation (with pathologic confirmation) of a detailed family medical history is the key to determining if a patient may be at increased risk for specific tumors. Once identified as being high-risk, these patients may be appropriate for earlier or more frequent cancer screening, lifestyle change, investigative chemoprevention, or prophylactic surgery.

Identifying patients at risk for an inherited predisposition to cancer

An estimated 15% of all cancer patients have an inherited risk[1]. The proportion of inherited cases for each specific type of cancer varies: 5% of ovarian cancer; 25% of medullary thyroid carcinoma; and 40% of retinoblastoma[2]. To best assess a patient's risk for an inherited predisposition to cancer, it is essential to accurately detail a family medical history. This history should include the following information:

- tumor or cancer
- primary tumors only (not metastatic sites)
- cell type
- age at diagnosis
- bilateral vs. unilateral
- multifocality
- relationship of individual to your patient
- tumor status of relatives from three generations
- other medical history/genetic disorders
- benign tumors (fibroids, polyps, cysts), goiter and other endocrine abnormalities, unusual skin findings, precancerous adenomas

The family history should be updated annually or when there have been significant changes.

Indicators that families have an inherited predisposition to cancer/tumors include the following:

- two or more family members from the same side of the family with an early onset cancer.
- three or more family members, on the same side of the family, with the same type of cancer regardless of age of onset.
- multiple primary tumors in the same individual
  - bilateral
  - multifocal
    - different sites, example: renal cell carcinoma and cerebellar hemangioblastoma
- a pattern of tumors often seen together in a genetic syndrome:
  - see breast and colon section for patterns often seen with those tumors
  - medullary thyroid carcinoma, hyperparathyroidism due to a parathyroid adenoma, pheochromocytoma (MEN2)
  - the 3 "P's" - pituitary, pancreatic and parathyroid tumors (MEN1)
  - melanoma and pancreatic cancer (hereditary melanoma)
  - cerebellar spinal and ocular hemangioblastomas, renal cell carcinoma, endolymphatic sac tumors (hearing loss), pheochromocytoma, epididymal/ renal/pancreatic cysts, pancreatic islet cell tumors (von Hippel-Lindau disease)

Individuals with these syndromes may not have all the defining tumors in the syndrome. However, each syndrome has its own recommended surveillance and medical management recommendations. Evaluation of affected or at risk patients is best performed in an established hereditary cancer clinic with expertise in this area. Generally, these clinics are consultative only, and refer patients back to their primary care physicians for recommended surveillance and medical management.

Inherited risk for cancers/tumors other than breast and colon cancer

Melanoma, papillary renal cell carcinoma, retinoblastoma, leukemia/lymphoma associated with immunodeficiency disorders and chromosome instability syndromes, multiple endocrine neoplasias (MEN1, MEN2), and von Hippel-Lindau disease are disorders for which causative genes are known.

Melanoma

Melanoma occurrence is on the rise in the United States, with a lifetime risk for the Caucasian population of 1%. Approximately one in ten individuals with melanoma has an inherited predisposition to this cancer. One in four or five melanoma patients with an inherited predisposition has been found to harbor heritable alterations in tumor suppressor gene p16, or in the proto-oncogene CDK[3,4]. Because hereditary melanoma manifests as an autosomal dominant pattern of transmission, it is often seen in multiple generations. Offspring of individuals with a constitutional (germ line)

alteration in a predisposing melanoma gene have a 50% chance of inheriting the alteration. Families with two or more cases of melanoma on the same side of the family; or a combination of relatives in several generations with dysplastic nevus syndrome (an individual with greater than 50 atypical moles) and/or melanoma; or families with a clustering of melanoma and pancreatic cancer on the same side of the family suggest the presence of an inherited predisposition[5,6,7]. Patients with an increased risk for melanoma should avoid sun exposure, use sun screen liberally, and undergo careful skin examination beginning in early childhood[8].

Papillary renal cell carcinoma

Approximately 4% of all renal cell carcinoma is heritable. The papillary variant of renal cell carcinoma accounts for 14% of all renal cancer cases and is the most frequent inherited renal cell histology. Clustering of papillary renal cell carcinoma in a family often occurs in an autosomal dominant pattern of inheritance and is associated with an alteration in a gene called MET (a proto-oncogene). Offspring of individuals with a MET alteration have a 50% probability of inheriting that alteration and thus having an increased risk of papillary renal cell carcinoma[9]. Inherited predisposition to non-papillary renal cell carcinoma can be associated with von Hippel-Lindau disease or a translocation involving chromosome 3p14, a heritable chromosomal abnormality[10].

Retinoblastoma

The childhood eye tumor, retinoblastoma, has an inherited etiology in 40% of cases. The gene responsible for retinoblastoma is the tumor suppressor gene, RB. Virtually 100% of bilateral cases of retinoblastoma (average age of onset is eight months) are of genetic etiology, as are 10-15% of sporadic unilateral cases (average age of onset is two years of age). Only 90% of those with an alteration in the RB gene develop retinoblastoma. Due to this reduced penetrance and to the occurrence of new RB gene mutations, there may not be a positive family history in an individual with a genetic form of retinoblastoma. Genetic testing can be performed postnatally as well as prenatally[2]. In view of the complexity of the genetics of retinoblastoma, genetic counseling is recommended for all individuals. At risk individuals should begin surveillance at birth.

Leukemia/lymphoma

Individuals with inherited immunodeficiency disorders[11,12] and chromosome instability syndromes are at increased risk for leukemia and lymphomas. The known chromosome instability disorders (e.g. ataxia telangiectasia, Bloom syndrome and Fanconi anemia) are autosomal recessive, hence a family history is often negative, although siblings of the proband may be affected.

Multiple endocrine neoplasias

Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant disorder. The gene responsible for MEN1 is known as menin. Tumors associated with MEN1 include pituitary (30%), parathyroid (95%), and pancreatic islet cell (41%). Most of the tumors are adenomas. Malignant potential of the tumors, especially those of the pancreatic islet cell, is of concern. Other adenomas, lipomas and carcinoids are occasionally seen in families. It is important to identify individuals who have MEN1[13,14], as appropriate medical management includes annual biochemical screening, careful radiological assessment and prompt surgical intervention when tumors are detected[15,16,17].

Multiple endocrine neoplasia type 2 (MEN2) is associated with a genetic abnormality in the RET proto-oncogene. One hundred percent of MEN2a patients have medullary thyroid carcinoma/C-cell hyperplasia, 50% have pheochromocytoma, and 10%-25% have hyperparathyroidism. MEN2b patients have medullary thyroid carcinoma, pheochromocytoma, oral mucosal neuromas, ganglioneuromas and in some cases a marfanoid habitus. Medullary thyroid carcinoma and pheochromocytoma are often bilateral in individuals with RET alterations[19]. Familial medullary thyroid carcinoma (FMTC) includes families with a RET gene mutation and medullary thyroid carcinoma/C-cell hyperplasia, but without any other tumor manifestations. Approximately 25% of sporadic cases of medullary thyroid carcinoma (MTC) are due to RET gene mutations, hence genetic testing for sporadic MTC may be appropriate if accompanied by genetic counseling. The sensitivity of RET testing is less than 100%, hence a negative result cannot eliminate the possibility of mutation in a sporadic case[18]. If a sporadic case is determined to have an abnormality in the RET gene, others in the family can then be tested. At risk individuals should undergo annual biochemical screening and thyroidectomy as appropriate[20]. Genetic testing of high risk children is recommended because thyroid cancer can occur in very young children. Some clinicians recommend prophylactic thyroidectomy in children with a diagnosis of MEN2 /FMTC[21].

Von Hippel-Lindau disease

The diagnosis of von Hippel-Lindau disease (VHL) should be considered in patients with a family history of pheochromocytoma, clear cell renal carcinoma or cerebellar/spinal/ocular hemangiolblastomas, or a personal history of an endolymphatic sac papillary tumor. Endolymphatic sac tumors often manifest as hearing loss. A clustering of several of these tumors in the same individual or in two or more individuals on the same side of the family is also significant. In addition to the above tumors, patients with VHL often have cysts in the pancreas, epididymis, and kidney. Onset of retinal tumors can be congenital, and other tumors may manifest in early childhood. Prenatal and postnatal genetic testing is available[22,23,24]. The gene responsible for VHL is the VHL gene on chromosome 3. It is inherited in an autosomal dominant pattern[25]. Surveillance of at-risk individuals begins at birth. Biochemical analysis, MRI's ,CT's, ultrasound, opthalmological and audiology examinations are all recommended, commencing at different times[26].

Cancers for which genes are unknown, or the approximate chromosomal location is known

Prostate cancer, leukemia

Prostate cancer

Approximately 10-20% of men will develop clinically apparent prostate cancer in their lifetime. Nine percent of all prostate cancer and 40% of all early onset prostate cancer (under age 55) is estimated to have an autosomal dominant pattern of inheritance. Early surveillance for prostate cancer is recommended for this high risk group[27], but general population screening is still controversial. Indicators of an inherited predisposition to prostate cancer include:

- the patient or one family member diagnosed with prostate cancer before age 55
- two or more relatives, same side of family (maternal or paternal), diagnosed with prostate cancer

A gene has yet to be discovered for inherited prostate cancer, but a candidate gene, hereditary prostate cancer 1 (HPC1), is localized to chromosome 1q24-q25[28]. There is a suggestion that prostate cancer families linked to the chromosome 1 gene abnormality may also be at risk for other types of cancer[29]. Because susceptibility to prostate cancer may be inherited in an autosomal dominant pattern, it is important to document the history on both the maternal and paternal sides. A woman can inherit an alteration in a gene that predisposes men to prostate cancer, and, while she obviously will not develop prostate cancer, she can pass that allele to either sons or daughters. Sons and grandsons who inherit the abnormality are at increased risk for prostate cancer. Therefore it is as important to document cases of prostate cancer in maternal uncles, maternal grandfathers and maternal cousins as it is in fathers and their male relatives.

Leukemia

Familial clustering of leukemia is rare. In a few families, an autosomal dominant pattern of inheritance has been demonstrated. Researchers suspect that there are heritable predisposing genes for acute myelogenous leukemia and myelodysplasia on chromosomes 9, 16, and 2[30]. Leukemia and lymphoma are associated with the autosomal dominant Li-Fraumeni syndrome[2].

Cancers for which familial occurrence is suggested, but causative genes are unknown

Lung cancer, testicular cancer

Lung cancer

One in 8 smokers and 1 in 2000 non-smokers will develop lung cancer in their lifetime. The risk for lung cancer is higher among both non-smokers and smokers who have a family history of the disease. Statistical analysis of lung cancer families suggest an autosomal dominant pattern of inheritance[31]. Researchers at the University of Colorado Health Sciences Center, in collaboration with other institutions, are attempting to locate a predisposing gene. At risk families have the following characteristics:

- two or more relatives on the same side of the family with lung cancer
- early onset lung cancer (before age 55)
- non-smokers with lung cancer
- individuals with Li-Fraumeni syndrome

(The University of Colorado [303 329-3066 or 800 473-2288] is interested in study participants, either affected or unaffected, from families with two or more cases of lung cancer.)

Testicular cancer

Testicular cancer has been observed in some sibships, suggesting an autosomal recessive pattern of inheritance[32]. However, only a small proportion of individuals with testicular cancer have an inherited risk and a gene has not been identified for heritable testicular cancer. Indicators of an inherited predisposition of testicular cancer that may warrant additional medical management include:

- bilateral tumors
- two or more siblings with testicular cancer

Summary

A genetic etiology has been discovered or postulated for many types of tumors, including breast, colon, prostate, lung, ovarian, renal, pancreatic, testicular, thyroid and uterine cancers, retinoblastoma, sarcoma, leukemia, lymphoma, brain tumors, and endocrine. The list continues to grow as researchers learn more about genetic risk factors for cancer, identification of which should lead to improved detection and cancer prevention in high risk individuals.

Careful analysis of an accurate family medical history facilitates identification of patients at increased risk for cancer. Genetic counseling and perhaps genetic testing may be appropriate when a physician encounters a family with the following characteristics: multiple members having the same type of tumor; multiple members having specific patterns of tumors; early onset cancer; or rare tumors suggestive of an inherited predisposition. Patients at increased risk for neoplasia require specialized surveillance and medical management.

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Cancer Genetics Services in the Mountain States Region

Arizona	
The Familial Cancer Program at the Mayo Clinic Scottsdale	602 301-7050
University of Arizona Health Sciences Center (Tucson)	520 626-2152
Colorado	
The Hereditary Cancer Clinic at the University of Colorado in Denver	800 473-2288 (information) 303 372-1880 (appointments)
Penrose Cancer Center, Hereditary Cancer Service in Colorado Springs	719 776-5274
New Mexico	
University of New Mexico Health Sciences Center	505 272-6611
Utah	
Huntsman Cancer Institute at the University of Utah	800 488-2422 or 801 581-6365
Information about local clinics is available from the National Cancer Institute	**800 4-CANCER**

Glossary

Autosomal disease - a disease encoded by a gene on a non-sex chromosome

Candidate gene - a gene thought to be a disease-causing gene, which maps to a region known to be linked to the disease

Carrier - an individual who carries one copy of a defective gene

Dominant (trait) - a condition expressed in individuals who have one copy of a defective gene

Expressivity - the degree to which a mutant gene is expressed; variable expressivity is characteristic of autosomal dominant diseases

Familial - any trait that is more common in relatives of an affected individual than in the general population; could be of environmental and/or genetic cause

Genetic screening - testing on a population basis for a genetic trait

Heterozygote - an individual who has two different forms of a gene at a given locus; i.e., different forms of a gene on two homologous chromosomes

Homozygote - an individual who has two identical forms of a gene at a given locus; i.e., the identical form of a gene on two homologous chromosomes

Linkage - the close physical association of two different genes, such that they tend to be inherited together

Missense mutation - a single DNA base pair change which results in a different amino acid coded for in a protein

Multifactorial inheritance - due to the influence of multiple genes and environmental influences

Mutation - a permanent genetic change in the genetic code of a person

Nonpenetrance - absence of signs of a disease usually caused by mutant gene(s); penetrance is an all-or-none phenomenon

Nonsense mutation - a single DNA base pair change which results in a premature stop codon; a truncated protein may be produced

Oncogene - a gene derived from a proto-oncogene, only one copy of which is necessary to cause cancer (e.g. RET gene mutation in MEN2)

Penetrance - the observable expression of a mutant gene

Point mutation - substitution of one DNA base pair for another

Polygenic diseases - caused by the influences of multiple genes

Polymorphism - the normal, i.e., non-disease causing, variation of DNA

Proband - the affected individual in a family who first comes to medical attention

Proto-oncogene - a normal gene which undergoes change to become a cancer causing gene (oncogene)

Recessive (trait) - a condition which is expressed only in individuals with two copies of a mutant gene

Tumor suppressor gene - a normal gene, both copies of which must be lost to cause cancer. Individuals from a cancer syndrome family may inherit the "absence" of one copy of the gene, and when the second copy is lost randomly in life, cancer can occur (e.g. the retinoblastoma gene); most familial cancer syndromes are associated with tumor suppressor genes

Web sites featuring information about hereditary cancers

American Cancer Society ..... www.cancer.org/frames.html

CenterWatch - Clinical Trials Listing Service ..... www.centerwatch.com/

Guide to Internet Resources for Cancer - University of Newcastle ..... www.ncl.ac.uk/~nchwww/guides/clinks1.htm

Healthfinder - a consumer health and human services information web site ..... www.healthfinder.org/default.htm

Huntsman Cancer Institute ..... www.hci.utah.edu

National Cancer Institute ..... www.nci.nih.gov

OncoLink ..... www.oncolink.upenn.edu

A general (and interesting) site for more information about the genetics of cancer ..... www.cancergenetics.org

Research

A Cancer Genetics Research Opportunity

The Rocky Mountain Cancer Genetics Coalition (RMCGC) is one of eight centers funded by NCI to develop a national cancer registry known as the Cancer Genetics Network. The RMCGC is composed of researchers at the University of Utah's Huntsman Cancer Institute, the University of Colorado Health Sciences Center and the University of New Mexico Health Sciences Center. The network will become a national resource for collaborative investigations into the genetic basis of cancer susceptibility by identifying and pre-assembling large and diverse populations of individuals who have had cancers, as well as their family members. It will also help health care providers address the ethical and psychosocial issues that affect healthy individuals and their families who may carry cancer susceptibility gene mutations. NCI will also support pilot studies on cancer genetics and foster collaborative research among participating institutions. To receive further information about the Cancer Genetics Network, interested individuals may call the Huntsman Cancer Information Service at 801 581-6365 or 800 488-2422.

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