Relative Risk

The Role of the Pedigree in Cancer Management and Risk Assessment

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PHOTOGRAPH/FOTOLIA

FAMILY HISTORY should be a key component in the management of cancer patients and their families. A recent study of 36,000 U.S. households found that many respondents had at least one first-degree relative with breast (7.74 percent), lung (7.10 percent), colorectal (4.96 percent), prostate (4.68 percent), or ovarian cancer (1.79 percent).[1] Approximately five to ten percent of all cancer in the United States has some significant hereditary component, and it is likely that more patients have at least some familial predisposition to cancer.[2] Family history may influence the likelihood that a patient will develop a second primary cancer either in the same or different organ system, and can also identify relatives who require extra-ordinary cancer screening or who should consider prophylactic surgery. The United States Preventive Services Task Force has recommended that patients at high risk for carrying a BRCA gene mutation should be referred for genetic counseling and possible testing.[3]

Many cancer centers and physician offices routinely collect information about family history, usually in the form of a checklist rather than a pedigree. However, family history information may not be consistently incorporated into management and risk assessment, referral for genetic counseling, or properly interpreted.[4,5,6]

Challenges Related to Genetic Testing

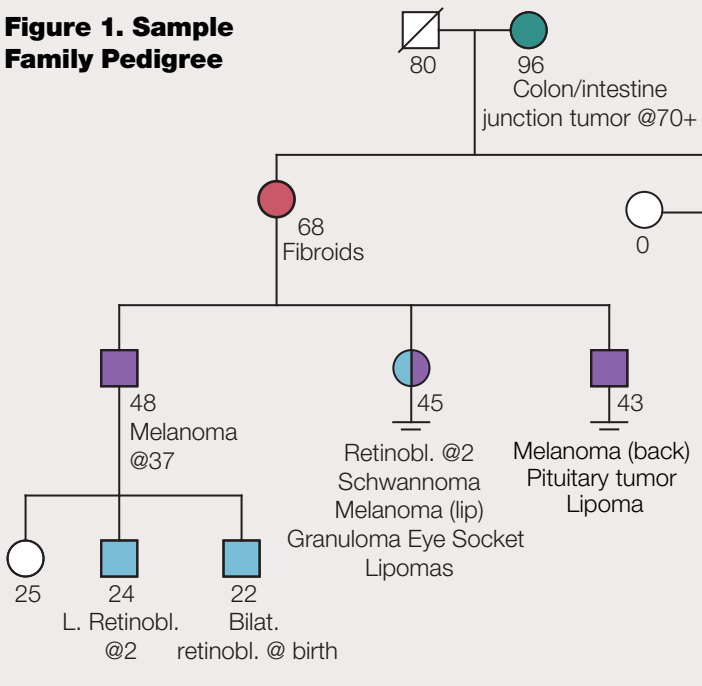
A pedigree allows for the presentation and storage of complicated clinical and genetic information in a clear and concise format,[7] and can provide key information to help manage and prevent cancers. However, it is critical that the information about the family history be properly collected and interpreted. In my view, every patient chart should contain a thorough family history, ideally in the form of a pedigree that is updated annually. Review of all family histories by a genetic counselor, medical geneticist, or nurse geneticist can help assure that genetic information can be properly integrated into patient care.

The emotional impact of genetic testing can be as great as the medical impact.[8,9] Genetic counseling touches on the very core of our patients' psyches, such as death, suffering, guilt, and worry about loved ones. In addition to specialized genetics training, healthcare providers involved in genetic testing and counseling need to have basic counseling skills to help ensure that the possible emotional and psychological harm of genetic testing does not offset its medical benefits.

Another concern of many patients considering undergoing genetic testing is the possibility of health insurance discrimination if an otherwise healthy person is found to carry a cancer-predisposing gene mutation. Fortunately, health insurance discrimination based on genetic test results appears to be very uncommon in the United States. However, many patients forego potentially helpful testing because of misinformation about health insurance discrimination.[10] Healthcare providers need to educate themselves and their patients about the risks of insurance discrimination, and work with legislators to help ensure that genetic test results are not used to deny patients access to health insurance.

The following case studies, which are drawn from my clinical practice, illustrate how a careful family history

Figure 1. Sample Family Pedigree



can influence the care of cancer patients and their families. Some of the details of the family and case histories have been slightly modified to protect patient confidentiality.

Case Study 1: Establishing a Correct Diagnosis

CC was a 40-year-old woman who had been referred to a gynecologist because she was requesting hysterectomy for uterine fibroids. Two years prior, she had undergone unilateral nephrectomy after she had been diagnosed with renal cell carcinoma. Because of the patient's habitus, the gynecologist recommended waiting one year so that the patient could lose weight to optimize the safety of hysterectomy. However, the patient alerted the gynecologist to her family history (see Figure 1), which included six relatives with retinoblastoma, as well as other relatives who had been diagnosed with uterine leiomyosarcoma and melanoma. Of particular note, when the patient was treated for renal cancer, she had alerted several physicians to her family history, all of whom were not concerned because, in the patient's words, "I told them I wasn't going to have any children."

After reviewing the patient's family history, I concluded that the pedigree was consistent with familial retinoblastoma due to mutations in the RB1 gene. Indeed, further investigation revealed that some relatives had previously had genetic testing at an out-of-state laboratory and were found to harbor a deleterious RB1 gene mutation. Familial retinoblastoma is associated with an increased risk for other tumors, including leiomyosarcoma but not renal cell carcinoma.[11] This information prompted review of the patient's renal tumor blocks, which had initially been analyzed at another institution. The review revealed that the tumor was in fact a rare renal leiomyosarcoma, thus suggesting that the patient was a carrier for the familial RB1 mutation. The new finding prompted greater concern about the management of her uterine fibroids because it can be difficult to distinguish between uterine fibroids and leiomyosarcoma by imaging studies. The patient and her gynecologist decided to perform the hysterectomy immediately, rather than delaying one year.

Case Study 2: Proper Assessment of Carriers of Gene Mutations

BK was a 35-year-old woman who had been recently diagnosed with invasive breast cancer. The patient is adopted; the only member of her biological family known to the patient was a twin sister (of unknown zygosity). Because of BK's diagnosis, her sister underwent screening mammography, which was normal. Based on BK's young age and lack of knowledge of her family history, BRCA gene testing was performed and showed that the patient carried a deleterious mutation in BRCA1. As the patient's sister had at least a 50 percent risk of carrying this gene mutation (assuming they are dizygotic twins), she underwent genetic counseling and testing, and was found to carry the same BRCA1 mutation. Because of the increased sensitivity of breast MRI in high-risk populations,[12] BK's twin was urged to have additional imaging studies. The MRI, performed less than two months after the normal mammogram, in fact showed that the twin also had an invasive breast cancer, and treatment was immediately initiated.

Case Study 3: The Risk of Occult Neoplasia

RV was a healthy 56-year-old woman who was the only successful tissue match for an adult child in need of a renal transplant. Based on her strong family history of breast and ovarian cancer, the transplant team was reluctant to use the patient as a donor due to concerns about transplanting a kidney with possible renal metastases.

The patient had a breast MRI, mammogram, ovarian sonogram, and serum CA-125, all of which were normal. Because of continued concerns about her hereditary risk, however,

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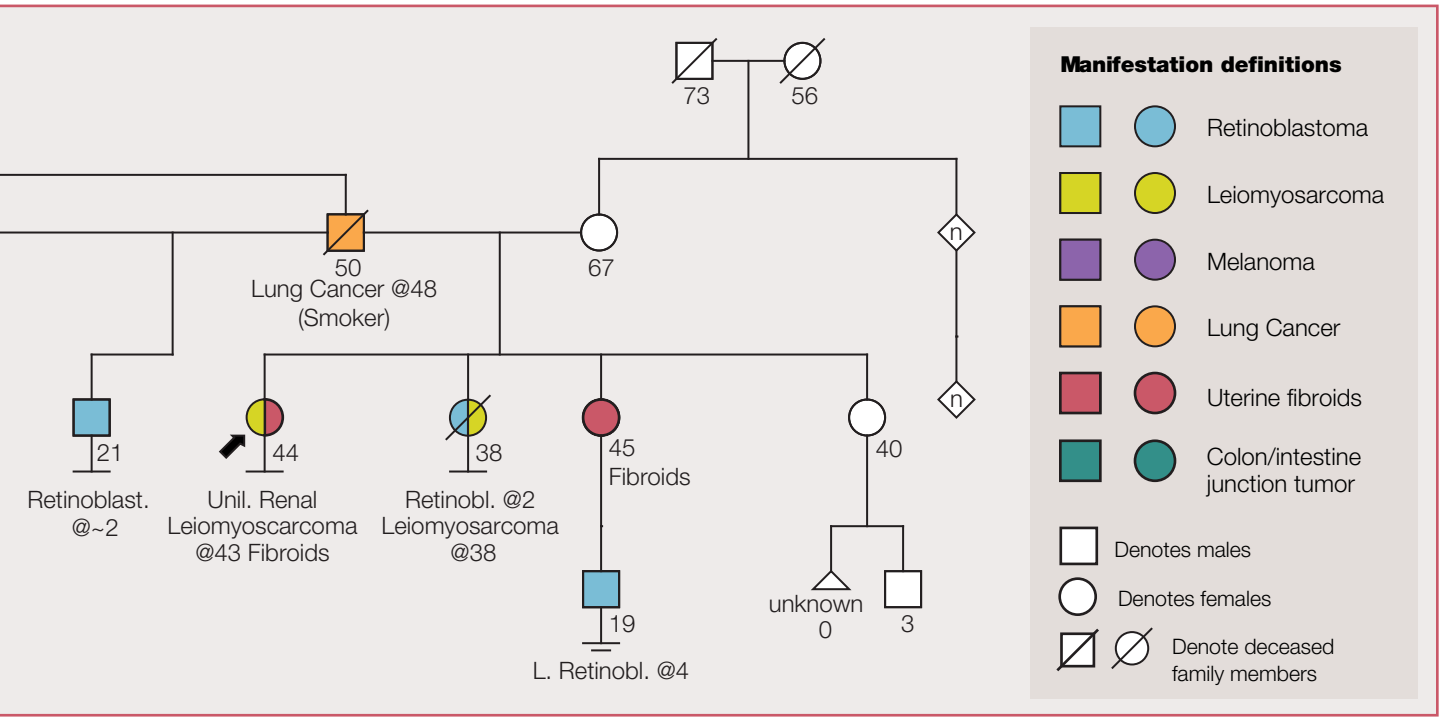

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discussions about BRCA testing were initiated with one of RV's sisters who had been diagnosed with premenopausal breast cancer about 15 years ago. The sister agreed to genetic testing, and was found to carry a BRCA mutation.

RV underwent testing, and was found to carry the same mutation. Because of the increased risk of ovarian cancer associated with BRCA mutations and the risk of occult ovarian neoplasia that has been identified in such women,[13] the patient underwent a risk-reducing salpingo-oophorectomy with rigorous pathological examination of the fallopian tubes and ovaries. A small focus of neoplasia was discovered in the tubal fimbria. The patient elected to undergo chemotherapy because of the small risk of occult metastatic disease. The renal transplant was delayed until the patient completed chemotherapy and shown to be completely disease-free.

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