



Your Family History Can Save Your Life

Timothy A. Donlon PhD, FACMG

Introduction

A look into the past is the best way to predict the future when it comes to common diseases, such as cancer. This article was originally intended to aid the Physician in assessing his/her patient's risk of developing cancer, however it became clear that cancer can affect anyone. Cancer results from both genetic and environmental causes. We may not be able to eliminate all the environmental causes but by knowing which diseases we're at most risk we can focus our energies on strategies that will have the most impact. The family history offers us a glance at our genetic make-up and can tell us much about our own personal health risks.

Taking a Family History

The American Medical Association now recognizes the importance that a family history plays in health management. They have put together a brochure and tools at: <http://www.ama-assn.org/ama/pub/category/2380.html>. A drawing of a family tree is called a "pedigree". Instructions can be found at <http://www.nsgc.org/consumer/familytree/index.asp>. You can keep a copy of this for your physician or other family members. Remember that this information is the most personal in nature and may cause anxieties in others who don't wish to know. Problems that may be encountered in constructing a pedigree include difficulty contacting relatives with whom one has little or no relationship, differing views between family members about the value of genetic information, resistance to discussion of cancer and cancer-related illness as the cause of deaths of relatives, unanticipated discovery of medical or family information (i.e. nonpaternity), and coercion of one relative by another regarding testing decisions. It is against the law in most states to discriminate against anyone based on their genetic make-up, except life insurance coverage.

On What to Focus

I'll use cancer as an examples. Begin the pedigree by writing down the medical information on:

- Proband (you or the person whose history you're taking)
- Proband's brothers (males are "squares") and sisters (females are "circles")
- Proband's children (in order of oldest to youngest, left to right)
- Proband's parents (father on left, mother on right)

Then go back a generation at a time and include:

- Nieces and nephews
- Aunts and uncles
- Grandparents
- Cousins

Collect the following specific information from each family member:

- Type of each primary cancer.
- Age at diagnosis for each cancer.
- Locations of malignancies.
- If the individual is still living, current age; if deceased, age at death and cause.
- Carcinogenic exposures (e.g., tobacco use, radiation exposure).
- Other significant health problems.
- Any surgeries that reduce the risk for cancer.
- Whether routinely screened for cancer.

If the information is unavailable, use your best guess (for example, "40's"). If you know the ethnic origins of the key family members it may help, as some diseases are more prevalent in certain groups. It is important also to consider whether there is nonpaternity involved or whether someone was conceived using assisted reproductive technology (e.g., donor egg or sperm).

Deciphering the Symbols

Deciphering a pedigree is truly an artform however, much can be gleaned from a cursory view. The clues are obvious when directly related family members are affected but even dominant forms of hereditary cancer can skip generations. For example, a male who carries a gene for breast cancer.

Suspicion should be raised by:

- Multiple cancers in close relatives, particularly in multiple generations.
- Early age of onset, younger than 50 years for cancers.
- Multiple cancers (primaries) in a single individual.
- Recognition of the known association between etiologically-related cancers in the family, such as breast with ovarian cancer or colon with endometrial.
- 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).
- Have a rare cancer, e.g., childhood adrenocortical carcinoma.
- Have an unusual presentation, e.g., right-sided colon cancer.
- Recognizable Mendelian patterns of inheritance (e.g. dominant or recessive).

Distinguish fact from fiction. Unless you have reliable verified information you should treat everything as hearsay. In such cases each individual item may not be as important as the collective pedigree.

Who's at Risk?

The table below shows the risk categories for common diseases. These are often associated with single (or a few) gene defects. In such cases, a single gene can have a large, profound affect on the patient's risk and the family history is usually obvious. About 5% of all cancers follow this pattern of inheritance. The remaining cases are less obvious but the pedigree can demonstrate clustering. Such cases are "multifactorial", being caused by combinations of genes that each have a small affect in addition to environmental factors (see Sporadic Cancers below).

Guidelines for Risk Stratification Based on Family History
High Risk
Premature disease in a 1 st degree relative
Premature disease in a 2 nd degree relative (multifactorial disease)
Two affected 1 st degree relatives
One 1 st degree relative with late or unknown onset and an affected 2 nd degree relative with premature disease from the same lineage
Two 2 nd degree maternal or paternal relatives with at least one having premature onset of disease
Three or more affected maternal or paternal relatives
Presence of a "moderate risk" family history on both sides of the pedigree
Moderate risk
One 1 st degree relative with late or unknown onset of disease
Two 2 nd degree relatives from the same lineage with late or unknown disease onset
Average risk
No affected relatives
Only one affected 2 nd degree relative from one or both sides of the pedigree
No known family history
Adopted person with unknown family history

Scheuner et al, 1997

What's the Risk?

Breast/Ovarian Cancer

Two commonly used models for predicting breast cancer risk are: the Claus model (Claus et al, 1994) and the Gail model (Gail et al, 1989). Both have limitations, and the risk estimates derived from the 2 models may differ for an individual patient. These models, however, represent the best methods currently available for individual risk assessment.

Colorectal Cancer

The most common forms of heritable colon cancer include Familial Adenomatous Polyposis (FAP), which is caused by a single gene on chromosome 5 and Hereditary Nonpolyposis Colorectal Cancer (HNPCC) which is caused by at least five genes involved in DNA repair. FAP is quite rare and generally has an early age-at-onset, and usually has a well-defined pattern of inheritance. HNPCC is much more common although the pattern of inheritance is not always obvious and the age-at-onset can be variable. HNPCC can be defined by the Amsterdam Criteria (Vasen et al, 1991) as having 3 individuals with colorectal cancer, 2 generations, of which 1 person is younger than 50 years, better known as the 3-2-1 rule. Revised criteria that consider extracolonic cancers have been developed and

include the Amsterdam criteria II (Vasen et al, 1999), the Bethesda guidelines, and the revised Bethesda guidelines (Rodriguez-Bigas et al, 1997).

Sporadic Cancers (Multifactorial Inheritance)

Breast cancer associated with BRCA1 and BRCA2 gene mutations is an example of inherited susceptibility. For most families susceptibility is transmitted along with many "low penetrant" genes that interact with environmental factors to modify the risk. These genes are exemplified by the Glutathione S-Transferase system that involves the detoxification of potentially carcinogenic agents. This system includes dozens of genes that work in a concerted manner, each having a specific role in detoxification. The GSTT1 null allele is nonfunctional but relatively common (>60% in Asians) and, by itself, includes only a modest increase (1.5 relative risk). A combination of variant alleles in three different GST genes results in a significant increase (9.93) in risk for breast cancer in premenopausal women in Finland (Mitrunen K 2001). Combinations of such genes are major factors in what appears to be "sporadic" cancer. Many other examples exist.

Glutathione S-Transferases and Breast Cancer Risk		
Gene(s)	Relative Risk	Frequency
GSTT1 null	1.5	15%
GSTT1 null + GSTM3*B	2.58	~8%
GSTT1 null + GSTM3*B + GSTP1 Ile/Ile	9.93	~6%

Mitrunen et al, 2001

Genetic Counseling and Testing

Genetic counselors are health professionals with specialized graduate degrees and experience in the areas of medical genetics and counseling. They provide information and support to families who may be at risk for a variety of inherited conditions. When testing occurs they incorporate pretest counseling, testing, posttest 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, finding support groups and patient resources, communicating with other specialists, and case documentation.

Genetic testing options can seem stifling for a non-geneticist health care professional. One role of the genetic counselor is to identify potential testing laboratories and to determine whether they're relevant to the present case. They can determine if a test has: analytic validity, clinical validity, clinical utility, and ethical, legal, and social issues that influence both validity and utility.

Getting More Information

A Genetic Counselor can be reached in Hawaii at either The Queen's Medical Center (537-7633) or Kapiolani Medical Center (983-8559). For information on constructing a family pedigree go to: <http://www.nsgc.org/consumer/familytree/index.asp>. For information on any genetic disease go to the database started by Dr. Victor McKusick; On-line Mendelian Inheritance of Man - <http://www.ncbi.nlm.nih.gov/> and select omim. Find genetics professionals in your area,

See FAMILY HISTORY, on p.249

contact the National Society of Genetic Counselors at www.nsgc.org; GeneClinics offers information on diseases as well as testing laboratories at www.geneclinics.org. To find more information about the medical conditions present in your family and about support groups, contact the Genetic Alliance at www.geneticalliance.org. To find answers to specific genetic forms of cancer go to: http://cancer.gov/search/genetics_services/.

For more information on the Cancer Research Center of Hawaii, please visit our website at www.crch.org.

References

1. Claus EB, Risch N, Thompson WD: Autosomal dominant inheritance of early-onset breast cancer. Implications for risk prediction. *Cancer* 73 (3): 643-51, 1994.
2. Gail MH, Brinton LA, Byar DP, et al.: Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. *J Natl Cancer Inst* 81 (24): 1879-86, 1989.
3. Mitrunen K, J. N., Kataja V, Eskelinen M, Kosma VM, Benhamou S, Vainio H, Uusitupa M, Hirvonen A. (2001). "Glutathione S-transferase M1, M3, P1, and T1 genetic polymorphisms and susceptibility to breast cancer." *Cancer Epidemiol Biomarkers Prev* 10(3): 229-36.
4. Rodriguez-Bigas M. A.; Boland, G. R.; Hamilton, S. R.; Henson, D. E.; Jass, J. R.; Khan, P. M.; Lynch, H.; Perucho, M.; Smyrk, T.; Sobin, L.; Srivastava, S.: A National Cancer Institute Workshop on Hereditary Nonpolyposis Colorectal Cancer Syndrome: meeting highlights and Bethesda guidelines. *J. Nat. Cancer Inst.* 89: 1758-1762, 1997.
5. Vasen HF, Mecklin JP, Khan PM, et al.: The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). *Dis Colon Rectum* 34 (5): 424-5, 1991. [PUBMED Abstract]
6. Vasen HF, Watson P, Mecklin JP, et al.: New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology* 116 (6): 1453-6, 1999.
7. Scheuner MT, Wang SJ, Raffel LJ, Larabell SK, Rotter JI. Family history: a comprehensive genetic risk assessment method for the chronic conditions of adulthood. *Am J Med Genet* 1997; 71: 315-324.

Classified Notices

To place a classified notice:

HMA members.—As a benefit of membership, HMA members may place a complimentary one-time classified ad in HMJ as space is available.

Nonmembers.—Rates are \$1.50 a word with a minimum of 20 words or \$30. Not commissionable.

For more information call (808) 536-7702.

Office Space

MEDICAL / DENTAL / HEALTHCARE RELATED — OFFICE SPACES AVAILABLE in Kalihi. Excellent location next to banks and restaurants at the corner of North King and Gulick in Central Honolulu Medical Clinic Building with air conditioning, free parking for patients and customers (41 total stalls), next to main bus line, competitive rates, and many patients. If interested, please contact Jan Kim at 441-0521 or 942-7100.

Seeking Internist

DEPARTMENT OF VETERANS AFFAIRS HONOLULU — has an opening for a FULL-TIME BOARD CERTIFIED INTERNIST to provide inpatient medical care to veterans hospitalized at Tripler Army Medical Center. Individual must demonstrate excellent clinical skills and have extensive experience in the field of hospital medicine. Responsibilities include direct patient care on the inpatient medical service, medical consultation on surgical and psychiatric services, and active participation as a faculty member in the Tripler internal medicine residency training program. VA and TAMC are affiliated with the University of Hawaii John A. Burns School of Medicine. Academic credentials should support a clinical faculty appointment. Individual must possess a full and unrestricted license in any state. Contact Human Resources Management Service at 808-433-0196, for an application package. Fax CV to 808-433-0391, attention Amy Duarte. Candidates are subject to physical examination and drug testing. An Equal Opportunity Employer.

Total Commitment to the Physician and Quality Health Care



Hawai'i Independent Physicians Association

Board of Directors 2004 Elections

Hawaii IPA's Board of Directors Elections are under way!

More than twenty candidates have come forward for the five seats that are up for election. Visit our web site at www.hipadocs.com for more details.

If you have not received your ballot by August 20th, please call Bill Donahue at 738-4472 or email him at wdonahue@hipadocs.com for a replacement ballot.

Office of Cancer Communications

National Cancer Institute

Pap Tests
A healthy habit for life!

Pap tests can help find cervical cancer at an early stage — while it's still easier to cure.

Call the National Cancer Institute's
Cancer Information Service at
1-800-4-CANCER (1-800-422-6237).

Visit NCI's website at <http://www.nci.nih.gov>