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## *In the Know*

### Connecting Patient / Family Library Patrons To Information, Ideas and Resources

July 2005

from

**The Duke Patient/Family Resource Center**

The Duke Patient/Family Resource Center is:

- A lending library offering books, audio and video tapes, magazines and free brochures dealing with cancer and certain blood disorders and with issues of coping, survivorship, caregiving, and grieving.
- Open 8:30 to 5:00 every day the Morris Clinics are open.
- Located in the White Zone, first floor, of the Morris Cancer Clinic, Room 15123.
- Our phone number is 919-684-6955. Our email address is [FamilyLibrary@mc.duke.edu](mailto:FamilyLibrary@mc.duke.edu)



**Resource Center Coordinator:** [Harriet Whitehead, PhD](#)

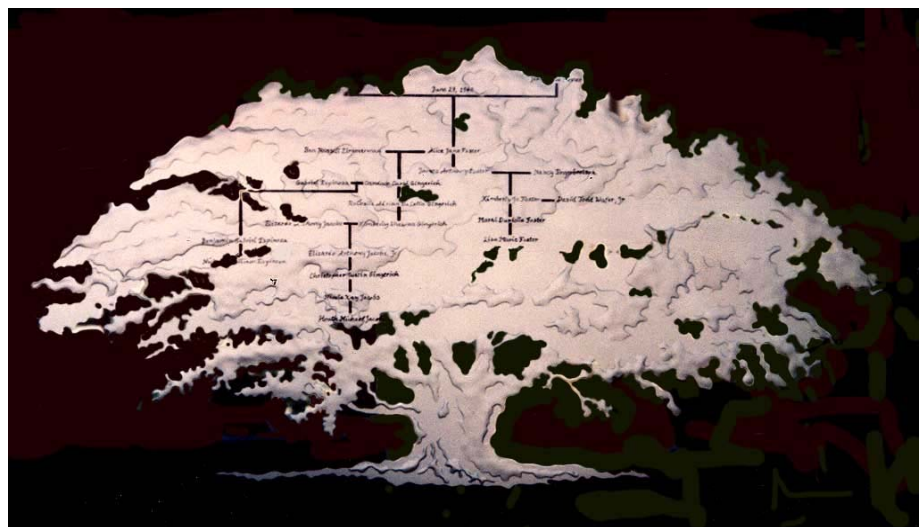
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## Genetic Testing for Cancer



[Graphic design by Alice Foster Zimmerman]

Cancer clusters in the family? Often a diagnosis of cancer sets patient and family members to ruminating. *How come there's so much cancer in this family? Two lung cancers - of course they were both heavy smokers. And all our uncles got prostate cancer; still, they were elderly men when they got it. But cousin Alice had breast cancer at age 50 and what did her mom die of? Ovarian? Uterine? One of those. And now I have breast cancer at 55 and my brother, who's 10 years younger than me, keeps getting these strange - like growths - on his face and neck...*

The numbers can build once you start thinking about it, and with this, the fear that a genetic time bomb is ticking away in your family. But what are the actual probabilities here? Who are the family members who need to start worrying and who are the family members who need to *quit* worrying? And is there any way to settle the matter once and for all?

We hope the information we provide in this issue of **In the Know** will enable our readers to get some clarity on the issue of inherited dispositions to cancer and some guidance on what settling the matter involves. We are very grateful to Robin King, our genetic counselor here at Duke, for collaborating with us on the issue. (Robin is on the right in this picture.) We would also like to thank Dr. Kelly Marcom, breast oncologist, for reviewing the newsletter.



### "Genetic" Cancers

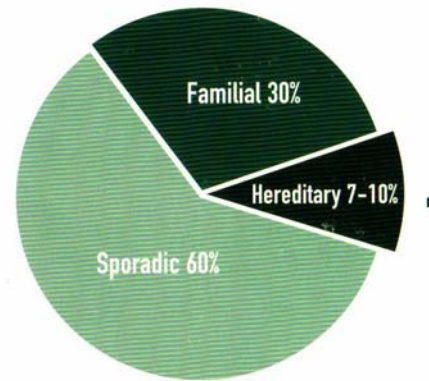
**Sporadic vs. germ line.** All cancers are genetic, but only some are *hereditary*. Another way to put this is that all cancers originate in genetic mutations, but only some of these genetic mutations can be passed along in the family line.

A handful of flawed genes in a single cell sets that cell on the cancer pathway, and it takes only one cell gone wrong to start a tumor. But most of the flaws in question occur randomly, through the routine wear and tear on our cells, or through exposure to environmental toxins, usually a bit of both. It will always take several mutations to produce a cancerous cell.

The "hereditary" cancers are those in which one or more genetic flaws were present at birth, inherited from one or both parents. These mutations are sometimes referred to as *germ line mutations*, while the normal non-inherited mutations that occur from wear and tear are called *sporadic mutations*. Should an individual start life with a germ line mutation, he or she is one jump ahead of the rest of us in getting cancer. It will still take several more mutations to produce a cancer, but this individual won't have to do quite as much living to arrive at the final step. Early age of onset is thus one of the factors that hints of a germ line mutation. The other main factor hinting of a germ line mutation is, of course, lots of cancer in the family, especially when these cancers follow a recognizable profile.

### Clusters and Their Profiles

Now let's return to the family that has noticed its "cancer cluster." The first thing they need to know is that most cancer clusters, whether they are in a family, or in a neighborhood, or in a workplace, do not arise from a common cause. Suspicious as it may look, the cluster can still be random, according to the statisticians. Even quite large clusters can be random, as trial lawyers who pursue workplace and environmental hazards, are beginning to learn.

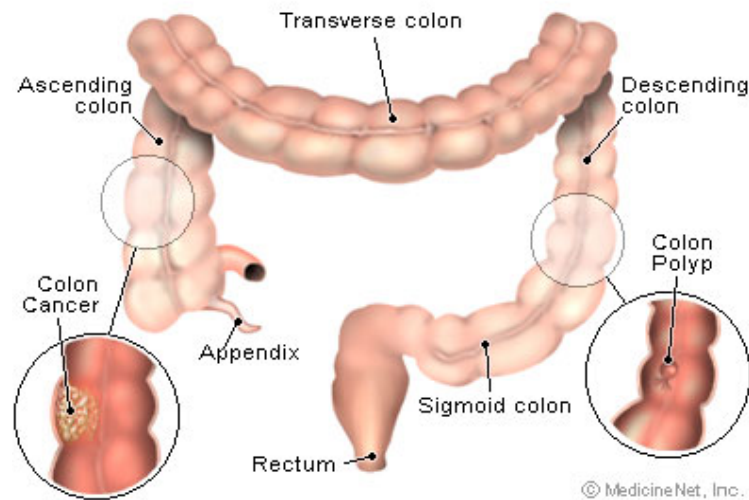


Total Sporadic and Hereditary Cancers

**Sporadic cancers and random clusters.** Moreover, geneticists now tell us that about 60% of all cancers *do not* involve a transmissible germ line mutation. They are sporadic. If the many cancers that are afflicting a family are predominantly among the elderly, or can be traced to a known carcinogen like tobacco, and if they do not follow a pattern of parent-child transmission over a generation or two, then it is very possible that the cluster is random and the cancers within it, sporadic.

**Heritable cancer syndromes.** What about the cancers that do not fall within this 60%? For a quarter of these (thus 10% of all cancers), geneticists can now affirm that germ line mutations are involved, and the profiles of how these mutations play out in a family history are available. Perhaps the most famous of these are the BRCA1 and BRCA2 gene mutations that are associated with a greatly elevated risk of breast and ovarian cancer, and a somewhat elevated risk for certain other cancers. Another well-known one is the mutation responsible for Familial Adenomatous Polyposis (FAP), which gives rise to multiple polyps in the colon, some of which will go on to become cancer if not removed.

I will give the specifics on these and several other germ line "syndromes" below. The point to bring out here is that once a cancer-causing germ line mutation has been identified, it fairly quickly becomes apparent that it produces a characteristic pattern of cancers and other health conditions - a distinctive syndrome. It does not produce just any old cancer. The syndrome may include very weird specifics. There is, for instance, a mutation that will produce thyroid cancer only of the medullary subtype. There is another that produces colon cancer predominately in the right ascending colon.



## Colon Cancer and Polyp

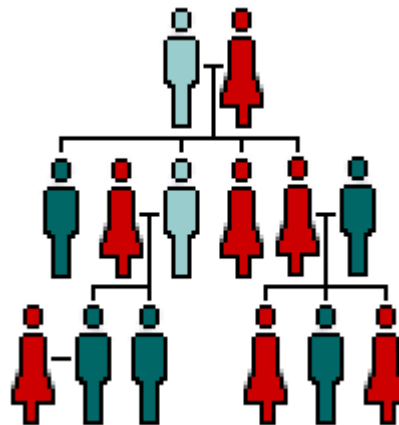
In this respect, the germ line causes of cancer tend to produce cancer clusters of distinct composition just as environmental carcinogens do. Vinyl chloride in the workplace, for instance, gives people brain or liver cancers (or certain other health problems), but not other cancers. Radon gases escaping from the earth into people's basements are linked to lung cancer, but not to other cancers.

**Familial cancers.** The 30% of all cancers so far unaccounted for are those over which there hovers a cloud of scientific suspicion. There's a transmissible look to them, that is, they can cluster in families, but so far no one has nailed down a crucial gene or genes. These are termed "familial" cancers. "Familial" is sort of a holding category, meaning "there's something going on here but we don't yet know quite what." It could be that people in an extended family with a high cancer rate have all been following an unhealthy lifestyle or living in an unhealthy area - hence the cancer cluster. But a genetic component cannot be ruled out. Many of the women who are now known to carry a BRCA mutation would, in the past, have been lumped in the "familial" category, while others of them, who could not produce much family evidence, would have been lumped in the "sporadic" category. Each time a new genetic syndrome is identified, the "familial" class of cancers loses some of its members to the "heritable syndrome" class of cancers.

In the example given at the beginning of our newsletter, our ruminator, who has breast cancer, is probably correct to eliminate the two heavy smoking lung cancer sufferers from her family cancer cluster. Their mutations, whatever the final package, certainly included mutations traceable to tobacco use. (She herself might consider this as a contributing factor to her breast cancer, not genes, if she has high tobacco exposure.) And generally speaking, a rash of prostate cancer among elderly uncles can be chalked up to the genetic flaws that occur with advanced age, not the sort of flaws that are inherited. The fact that "all our uncles" got it, raises some questions, but how many is "all"? A half-dozen could be disturbing. Three not so much, unless it combines with a number of other indicators.

But cousin Alice and her mother, if the mother was our ruminator's blood relative, might be worth a look, especially if it can be determined that Alice's mother indeed died of ovarian cancer. The ages 50 (for Alice) and 55 (for the ruminator) are not suspiciously early ages to get breast cancer, but they are not reassuringly late ages either. So there's a whiff of concern that the genetic flaw behind "breast/ovarian syndrome" may be present. If this is the case, the presence of a lot of prostate cancer in the family may tie in. There is a different syndrome that can produce breast and uterine cancer - "Cowden's syndrome." Here the growths on the brother's neck and face may take on significance.

**Some syndromes.** According to Robin King there are at least 200 known heritable syndromes, but most are too rare to concern us here. The following are the seven most common. All of those listed are mutations that are inherited dominantly. This means if one parent carries the mutation, there is a 50-50 chance the child will inherit it.

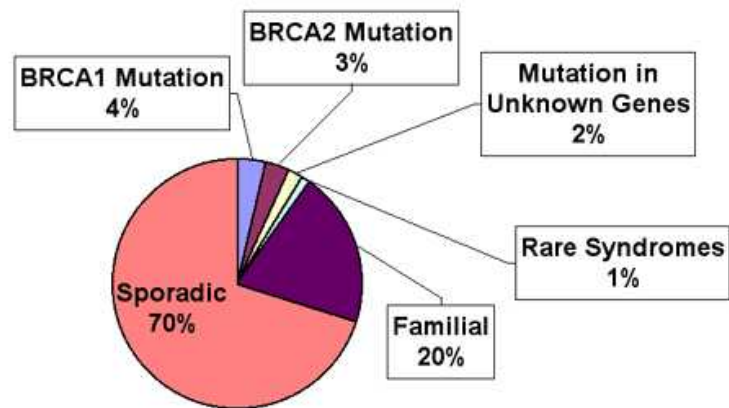


1. **Breast/ovarian syndrome.** Cancers cropping up in families with a germ line mutation in either the BRCA1 or BRCA2 genes will be primarily breast and ovarian. But prostate cancer, pancreatic cancer and even melanoma appear more commonly in affected families than in families without the mutations. Male breast cancer is often associated with BRCA2 mutations. Whatever the gender or cancer, age of onset for cancer will be younger than average for some affected persons. There may be at least one affected person who has more than one primary cancer, e.g. two separate breast cancers or breast plus ovarian. BRCA1 and BRCA2 are large genes and can mutate in some 200 ways such that they no longer produce a key protein involved in cell repair. The risk of cancer from them, in their mutated state, is close to 85%.
2. **FAP/Familial Adenomatous Polyposis syndrome.** Mutations in the APC gene causes the colon to develop dozens, hundreds, even thousands of colon polyps. Without medical intervention, some of these polyps will progress to cancer. Approximately 95% of those carrying the mutated gene will have multiple polyps by age 35, but polyps and cancer can occur as early as adolescence. Multiple health conditions, usually

- centering around benign growths elsewhere in the body, are associated with FAP. There is another multiple polyposis gene, called MYH, which is inherited recessively - both parents must be carriers. It is dangerous as well, but, at this point, less well understood.
3. **Lynch syndrome or HNPCC.** There are up to 5 genes involved in this colon cancer syndrome. It produces early onset colon cancers that are predominantly in the right ascending colon and predisposes individuals to a range of other primary cancers, mainly in the female reproductive tract or the urinary tract. Lynch syndrome carries about an 80% risk of developing one of the characteristic cancers. While Lynch does not produce the thousands of polyps that FAP often does, cancers from Lynch will be preceded by a polyp. Thus frequent screening could detect and remove the problem before it becomes a full-scale tumor.
  4. **Cowden syndrome** is caused by a mutation in the PTEN gene and is associated with breast, thyroid (the non-medullary type), and uterine cancer. The cancer risk is about 50%. An associated health condition is multiple acne-like papules in the head and neck area.
  5. **Li-Fraumeni syndrome (LFS)** arises from mutations in the p53 gene, one of our most crucial tumor suppressor genes. LFS comes the closest of all the syndromes to being a tutti-frutti cancer gene, because the range of cancers that can result is so wide. The most frequent cancers are sarcoma (soft tissue or bone cancers), breast, leukemia, adrenal gland, and brain. Cancer risk is close to 100%. There are few if any associated non-cancer health conditions.
  6. **Von Hippel-Lindau syndrome.** This syndrome increases the risk for brain, kidney, and certain less common cancers. Risk of cancer about is 40%. An associated health condition is the proliferation of knots or tangles of small blood vessels in the brain, the adrenal glands, the spinal cord and other parts of the body.
  7. **Multiple Endocrine Neoplasia syndromes.** The MEN1 and MEN2 syndromes are named after the genes involved. We are concerned here mainly with the MEN2 subtypes. MEN2A is associated with an increased risk for thyroid cancer of the medullary type and for tumors of the adrenal gland. An associated health disorder is hyperparathyroidism. MEN2B is also associated with medullary thyroid cancer. Patients with this syndrome (2B) also show a variety of additional conditions: a characteristic facial appearance with swollen lips; tumors of the mucous membranes of the eye, mouth, tongue, and nasal cavity; enlarged colon; and skeletal abnormalities. The MEN2 syndromes carry a cancer risk of about 70%.

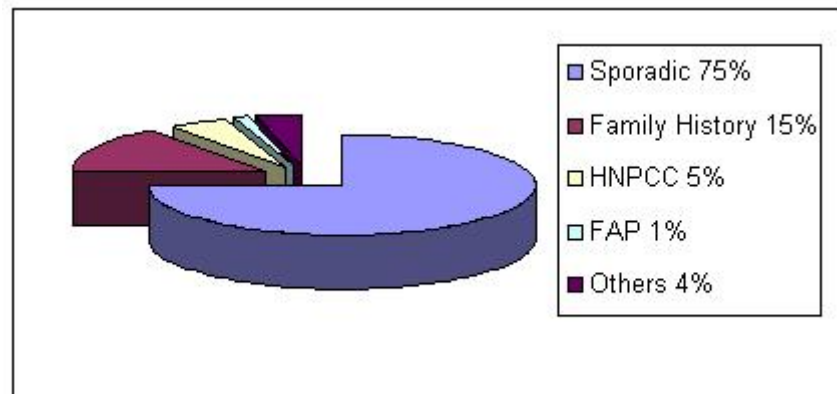
It is true that people with certain common cancers, such as breast or colon, have several syndromes to choose from here. This could incline them or their family members to worry excessively about a ticking genetic time bomb. It might help to be reminded of what a small percentage of any cancer is attributable to these syndromes. Here is a pie chart of breast cancer causes, for example.

## Breast Cancer Cases by Type

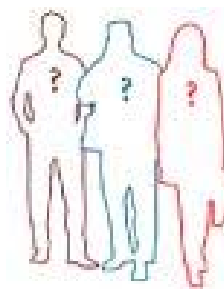


[Graphic provided by the University of Colorado Cancer Center]

Colon cancer's known heritable chunk of the pie is comparably small. Remember that "familial" cancer is not considered a truly genetic cancer until a gene is identified.



## Who Should Consider Genetic Testing and How Does it Work?



A family should explore genetic testing only if there is some useful follow-up intervention available should it turn out that a cancer-causing mutation is present. There is no point in learning the genetic story if there's nothing that can be done. And there is no point in spending money on gene tests, if the follow-up would be something that one is already permitted or urged to do,

such as have everyone in the bloodline screened for colon polyps should one family member be found to have thousands in his/her colon.

On the other hand, if the recommended follow-up involves

- the removal of vulnerable tissues and organs, e.g. colon, breasts, or ovaries
- an unusual and non-routine form of screening which would not normally be covered by insurance (such as MRI's of breasts, spiral CTs of lungs, or tumor marker tests)
- screening of such frequency or at such early ages that family members would find it burdensome (for example, colon screening in a possible FAP family should begin for everyone starting as young as 10 yrs old)

then it behooves the family to find out which persons, if any, carry the dangerous gene. Those persons alone, rather than the entire family, would be eligible for the follow-up procedures.

**Indicators of a heritable cancer.** A family should explore genetic testing if there are two or more of the following indicators present in their family history.

- Cancers occurring at an earlier than normal age
- Multiple generations affected by cancers
- Rare cancers appearing
- Individual(s) with multiple primary cancers

**Seeing a genetic counselor.** Many primary care physicians are not up on the latest genetic findings and may have misunderstandings about the role of your insurance company. Your oncologist will know more, but he/she may lack detail. It is usually best to start with a genetic counselor, like Robin King, who can lay out the entire drill for you and your family members. The genetic counselor is also the person who best knows how to deal with the various family dynamics and emotional reactions that appear when family members face the genetic cause issue.

**Commonly followed steps.** Your genetic counselor will begin by analyzing family history and probing the issue of whether useful follow-up procedures are available for the suspect cancers. You should be prepared to obtain precise information on all the cancers in the family (in the bloodline only, in-married persons don't count). Should procedures be available, and should there be at least some family members who want to follow these procedures, the next step would be to select an individual who has, or has had, one of the suspect cancers. His or her blood sample will receive the most wide-ranging genetic survey. While a wide genetic survey can be expensive, undergoing the test itself is not onerous. Typically one simply sends off blood to a lab.

Should the starting person test positive for a cancer-causing mutation, his or her test will reveal not only the source of the family problem, but the precise mutation that is being transmitted. In the case of certain syndromes, such as breast/ovarian, where up to 200 mutations of the BRCA genes can occur,

narrowing down the particular one that is being transmitted in a family can save enormous time and expense. All subsequent tests of family members will focus on this particular mutation and will therefore cost less.

**The role of the insurance company.** Contrary to popular opinion, most insurance companies do cover genetic testing, when indicated by your medical advisers, and they do not require that you tell them the results. Of course, they will know that you were advised to get tested. And if you want to undergo any of the follow-up procedures that are available for the mutation positive person, *and have these procedures covered by insurance*, then you will have to tell them the positive results.

It does not follow that they will raise your rates. In fact, for North Carolinians, there is a law on the state books that insurance companies cannot raise premiums or deny coverage based on genetic information. Check the situation in your state if it is not North Carolina. (There's a federal law working its way through congress that would protect everyone from genetic discrimination, but it hasn't passed yet.) Also, if you have group coverage anywhere in the country, there is a regulation that is part of the Health Insurance Portability and Accountability Act (HIPAA) that states that a person with a genetic predisposition to an illness but with no symptoms cannot be considered to have a "pre-existing condition."

The adult child of a person found to be positive for a cancer-causing gene should have no trouble obtaining normal insurance coverage, because his or her company would have no access, and no right of access, to the parent's information.

Things can be a little tougher on medicare and medicaid. Medicare pays for only two of the most established tests: the BRCA tests and the HNPCC tests. Medicaid, being a state program, will not pay for tests that are conducted out-of-state. This means that unless you live in Utah, where all of the BRCA tests are performed, medicaid will not cover them, and these are the most expensive, especially for that first-tested family member.

All of these remarks apply to medical insurance. Life insurance may be a different story, depending on your insurance company.

**Tests and costs.** Below is a list of the ball-park test costs and the recommended follow-up procedures for the syndromes discussed above. I will list only the costs of that expensive first person below. For every listed syndrome, testing for an already found mutation costs much less, around \$350. When I give an age at which to start screening gene-positive people for cancer, it will refer to the youngest age at which a cancer or its fore-running symptoms might occur. If positive for the gene, a person older than that would, of course, begin increased cancer screening at whatever age he/she is.

1. **Breast/ovarian cancer syndrome.** Testing the first person costs \$2975. Follow-up for positives: recommended that they start breast screening at an earlier age (late twenties) with both MRI and mammography. Clinical breast exams should be every six months. There is the option of

- mastectomy. Ovarian cancer screening is not very effective yet, so it is recommended that positive women have their ovaries removed after completing childbearing, around age 40. Men should start screening for prostate cancer at age 40, rather than 50, with annual PSA blood tests, and have annual physicals which include chest/breast exams.
2. **FAP/Familial Adenomatous Polyposis.** Testing the first person costs \$1685. It is recommended that colon screening start at ages 10-12. Once polyps appear, a complete removal of the colon is recommended. One should also screen for small bowel cancers with an annual upper endoscopy.
  3. **Lynch syndrome.** Testing the first person costs \$1950. Screening for colon cancer should start at an age 10 years earlier than the age-of-diagnosis of the first affected family member, or in the early thirties. Women should screen for uterine cancer through annual endometrial aspirations or biopsies, starting around the same designated age.
  4. **Cowden syndrome.** Testing the first person costs \$1400. Recommended are increased screenings for breast, thyroid, and uterine cancers. Increased means every 6-12 months.
  5. **Li-Fraumeni syndrome.** First person costs \$950. There should be increased screening for breast cancer, a baseline MRI of the brain and kidneys, and close attention and follow-up to any unusual symptoms.
  6. **Von Hippel-Lindau syndrome.** First person costs around \$900. Annual screenings would begin around age 16. An initial work-up that includes a neurological history and physical exam, audiologic examination for hearing loss associated with ear tumors, blood pressure determination, urine analysis, and abdominal ultrasound would kick things off.
  7. **Multiple Endocrine Neoplasia (MEN).** First person costs are about \$650 for MEN2A, and \$500 for MEN2B. Biochemical tests (blood, urine), performed more or less annually, would be used to screen for endocrine tumors. Usually it is recommended that the patient have their thyroid removed.

**Related resources.** For those who would like to know more about a particular test or procedure (e.g. MRI, endoscopy), please look up the September 2004 issue of **In the Know** under "previous issues" at this website, or click on the sidebar link on this website entitled "Tests and Procedures."

Brochures and videos on genetic testing are available at the Patient/Family Resource Center.

A well-illustrated explanation of hereditary cancers and genetic testing issues appears on the Cancer.Gov website at <http://www.cancer.gov/cancertopics/understandingcancer/genetesting/allpages>

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