



Genetic and Familial Factors Influencing Breast, Colon, Prostate and Lung Cancers

By Quinn P. Stein, MS, CGC; Jason D. Flanagan, MS, CGC

Abstract:

Knowledge of cancer genetics is advancing our biological understanding of breast, colon, prostate and lung cancers. A family history of any one of these four types of cancer can increase an individual's personal risk to also develop a malignancy. For some families, genetic testing, in combination with genetic counseling, can be a helpful way to identify a hereditary cancer predisposition gene or establish a cancer risk management plan. In this paper, we will review the current state of knowledge surrounding genetic factors influencing breast, colon, prostate and lung cancer.

Introduction

When caring for an individual with a current or past history of cancer, the role of genetic factors and family history cannot and should not be overlooked. Although most cancer develops sporadically, as much as 10 percent of cancer is thought to be inherited. This is significant since an inherited cancer predisposition gene not only increases the chance for a primary cancer but can also increase the chance for a secondary cancer and, thus, treatment may need to be altered.

Single genes influencing the development of breast and colon cancer have been known for more than a decade, with clinical genetic testing available. More recently, however, recommendations for cancer surveillance have been broadened to also include familial empiric risk factors, i.e., the number and ages of diagnoses of cancers in the family. In this paper, we will review the current state of knowledge surrounding genetic factors influencing breast, colon, prostate and lung cancer. We will also explore the genetic counseling process as a way to facilitate genetic testing and provide a familial cancer risk assessment.

Breast Cancer

Most cancers, including breast cancer, occur sporadically. Approximately 30 percent of the time, however, two or more family members are affected. When this occurs, the question to address is “Why are several cases of breast cancer seen in a particular family?” More generally, why do some families have more cancer in them than others? There are 3 possible explanations:

1. Chance;
2. A hereditary cancer gene mutation (e.g. BRCA); and/or
3. Shared genes/shared environment (sometimes known as familial cancer)

Hereditary Cancer

Several genes have been found to increase susceptibility to breast cancer when inherited in altered forms, but two specific genes influence risk more than all others. These two genes are known as BRCA1 and BRCA2. Both genes normally function as tumor suppressors, with the role of maintaining genomic integrity. Tumor-suppressor genes, or more precisely, the proteins for which they code, are important because of their role in DNA damage repair. Tumor suppressor genes follow the “two-hit hypothesis,” meaning that both alleles that code for a particular gene must be affected before a disease is manifested. If a person is born with one germline mutation, a “second hit” is still needed before cancer can develop. Those who possess a germline mutation in BRCA1 or BRCA2 are often said to have a “predisposition to cancer” or a “cancer susceptibility gene.”

The best tool to help identify families which may have a cancer susceptibility gene is an accurate family history. Health care professionals should recognize that family history is an intrinsic part of a comprehensive cancer risk assessment and as important as asking about other personal risk or environmental factors. Family history collection needs to go beyond first-degree relatives because an assessment of only first-degree relatives will not take into account paternal contribution. Also, it is a common misconception that only the mother's side of the family is important for breast cancer, when, in fact, both sides of a family history are important.

When looking at a family history, there are several “clues,” or characteristics, any one of which may suggest that a cancer susceptibility gene may be present. For breast cancer, these include:

- A) Multiple close family members affected with breast cancer or ovarian cancer;
- B) Earlier than average age at cancer diagnosis (under 50, or before menopause);
- C) Bilateral breast cancer;
- D) Breast and ovarian cancer in the same person;

- E) A specific pattern of inheritance;
- F) Rare or unusual cancers such as male breast cancer; and/or
- G) A tumor which is hormone receptor negative, high-grade and highly mitotic.

BRCA-related cancers are more likely to be high-grade, poorly differentiated and highly mitotic. They are also more likely to be estrogen receptor- (ER) and progesterone receptor- (PR) negative. In most studies the overall prognosis for BRCA-related cancer is similar to that of sporadic cancer, but the risk for a second breast cancer in BRCA mutation carriers is 20 percent to 40 percent over ten years. Many affected women will opt for prophylactic removal of the contralateral breast at the time of diagnosis. Thus, knowledge of BRCA status can directly impact cancer management. Advantages of this approach are a 97 percent risk reduction in contralateral breast cancer.¹

Knowledge of BRCA status is not only important to women diagnosed with cancer, but also to family members since those who possess a mutation are at significantly increased risk to develop both breast and ovarian cancer. Current data suggests that women who inherit one non-functioning copy of BRCA1 or BRCA2 have a lifetime risk to develop breast cancer of 50 percent to 85 percent and a 20 percent to 45 percent lifetime risk for ovarian cancer.² Because of these significantly increased risks, women possessing a BRCA gene mutation need to be more active with regard to surveillance and/or treatment than compared to women in the general population.

Current recommendations for women with a germline BRCA1 or BRCA2 gene mutation include monthly breast self-exams starting between ages 18 to 21, annual clinical breast exams starting between ages 25 to 35 and annual mammography starting between ages 25 to 35. More recently, it has been recommended that women also be offered breast MRI as an adjunct to mammography.³ Breast MRI is known to be more sensitive than mammography, therefore it can be a useful tool to detect breast cancer in young women, including BRCA mutation carriers. In addition, prophylactic bilateral mastectomy has been shown to reduce breast cancer risk by greater than 90 percent in women with a BRCA mutation. In our professional experience, many women in South Dakota do not originally initially opt for bilateral prophylactic mastectomy after they first find out they are BRCA positive. They will, however, often choose bilateral mastectomy as a surgical option later when diagnosed with a unilateral breast cancer diagnosis.

Ovarian cancer risk is also increased by a BRCA gene mutation, but unfortunately good screening methods for ovarian cancer remain elusive. Conversely, prophylactic bilateral

oophorectomy reduces ovarian cancer risk by 96 percent in women with a BRCA mutation. Oophorectomy is generally recommended after 35 years of age or after childbearing is completed. Additionally, if this procedure is performed pre-menopausally, it also reduces the risk of breast cancer by more than 60 percent.⁴

In general, BRCA genetic testing is considered a reasonable option for those individuals who have had cancer at young ages or whose family history is suggestive of a certain type of inheritance. The likelihood of the presence of a BRCA1 or BRCA2 mutation can be estimated by licensed genetic counselors. When a patient/family decides to pursue genetic testing, an affected relative is the best candidate in the family to be tested. It is best to first test an individual who has had cancer, whenever possible, in order to give the greatest chance of finding a mutation in the family. If a mutation is identified, usually by full gene sequencing, other family members at risk may be tested for just the known single gene mutation. This is significant, since sequencing currently costs several thousand dollars while known mutation testing costs only a few hundred.

Appropriate use of genetic testing, along with MRI and mammography, could improve breast cancer detection in young women. To date, almost all BRCA gene mutations detected have been familial rather than *de novo*. Identifying mutation carriers and testing unaffected women may identify high-risk women who should undergo additional screening and be offered preventative options.⁵

Familial Breast Cancer

In some families, the incidence of breast cancer is more than one would expect by chance alone, yet the family doesn't fit a clear a pattern of inheritance, and a single gene mutation is not identified. In these families, the cancer is said to be familial. These histories may be the result of small family size, skewed distribution of the higher-risk gender or multifactorial influences. For these families, genetic testing is less likely to be informative, yet the families may still be in need of increased surveillance if the risk is deemed to be "high."⁶ The cancer models BRCAPRO, Claus and Tyrer-Cuzick are often used by genetic counselors to help determine risk. All three models rely heavily on family history including both affected and unaffected relatives.

The American Cancer Society recommends screening by breast MRI for those women with a lifetime risk of 20 to 25 percent (or greater) of developing breast cancer. There is an increasing amount of literature demonstrating that breast MRI screening can identify cancer in patients of specific risk groups. Several studies have demonstrated the ability of MRI screening to detect cancer with early-stage tumors that are associated with better outcomes. While survival and mortality data are not yet available, it has been proven that

MRI has higher sensitivity and finds smaller tumors compared with mammography, and these types of cancers found with MRI are the ones that respond to therapy and that contribute to reduced mortality.³

Colon Cancer

Colorectal cancer is the third most-commonly diagnosed cancer in both men and women. It is estimated that 146,970 new cases are diagnosed annually, with 4 to 6 percent of these cases being caused by a hereditary cancer susceptibility gene.⁷ This sizeable disease burden is made even more complex by the fact that several different cancer susceptibility syndromes are associated with colon cancer. Some of these cancer syndromes include: hereditary non-polyposis colon cancer (HNPCC) which is also known as Lynch syndrome, familial adenomatous polyposis (FAP), attenuated familial adenomatous polyposis (AFAP), Muir-Torre syndrome, Turcot syndrome, Gardner syndrome, Juvenile polyposis syndrome, Peutz-Jeghers syndrome, PTEN hamartomatous syndrome and MYH-associated polyposis.⁸ Of these, HNPCC is the most common followed by FAP and AFAP.⁹

HNPCC

Although there are a number of inherited syndromes that can increase a person's risk of colon cancer, HNPCC is the most common. An estimated 3 to 5 percent percent of colon cancers are thought to be associated with HNPCC.⁹ The syndrome is caused by an inherited mutation in one of several DNA mismatch repair genes, namely MLH1, MSH2, MSH6 or PMS2. Mismatch repair genes are critical for the maintenance of genomic stability, because of their role in identifying and excising single-base mismatches and insertion-deletion loops that may arise during DNA replication. An inability to identify and repair the "mismatched DNA" makes it more likely that mutations will accumulate and set the stage for the development of cancer. Of the mismatch repair genes causing HNPCC, MLH1 and MSH2 are the most common accounting for approximately 90 percent of deleted mutations.⁹

A consequence of a cell's inability to repair DNA mismatches is a tumor variation known as microsatellite instability (MSI), in which simple repetitive sequences of DNA called microsatellites demonstrate characteristic changes in their length. MSI is found in about 90 percent of HNPCC related tumors, and, in fact, can be used as a screening method for HNPCC. It is important to note, however, that evaluating a tumor for MSI is a considered a screening test only, and not an actual diagnostic test.

Individuals who carry an inherited mutation for HNPCC are at greatly increased risk for colon cancer with an estimated lifetime risk of up to 80 percent. This diagnosis is often earlier than normal with an average age of 45 years,

compared to 65 years in the general population.¹⁰ The cancers are much more likely to be found in the right side of the colon. There is also a higher chance of developing a second colon cancer; risks are 30 percent over 10 years and 50 percent over 15 years.⁹

HNPCC is inherited in an autosomal dominant manner. Therefore, men and women are equally likely to have this disorder, and their sons and daughters are equally likely to inherit this disorder. A difference exists between sexes, however, in that women have the added potential burden of endometrial or ovarian cancers. About 40 to 60 percent of women will develop endometrial cancer during their lifetimes, and 12 percent will develop ovarian cancer.⁹ The average age of diagnosis of endometrial cancer is 46 years. In addition to the above mentioned increased risks for colon, endometrial, and ovarian, and colon cancers, both men and women with an HNPCC gene mutation are at increased risk for stomach cancer (13 percent).

For some time, HNPCC was a clinical diagnosis based solely on pedigree analysis and the Amsterdam criteria – which were initially formed for research purposes, but may have missed up to 40 percent of at-risk families.¹¹ At the present time, however, the majority of the genes associated with HNPCC have been identified, and clinical testing is available to help verify cancer risk status for family members. Genetic testing for the four known mismatch repair genes is thought to have a sensitivity of approximately 70 percent (Lynch).⁹ As with all hereditary cancer testing, when such a test is being considered in a family, initial analysis should be done on an individual who has had cancer so that it would be possible to correlate the genetic change with the occurrence of cancer.

Knowledge of a mutation in an HNPCC gene can be advantageous for individuals with and without prior histories of cancer. Because of its early age of onset, colonoscopy needs to start by age 25 and should be repeated every 1 to 2 years through age 40, and then annually thereafter. The reality that the cancers are most often found on the right side of the colon can be problematic. “Complete colonoscopies” are recommended but various studies have shown that only about 56 percent of colonoscopies can be considered “complete.”¹² Colonoscopies should be performed by specialists who have been made aware of the familial mutation, so that extra time can be spent on the right side of the colon. It has also been suggested that spiral CT be performed on individuals with HNPCC to better visualize the right side of the colon as well as to aid in detection of extracolonic cancers.¹² Should colon cancer occur, subtotal colectomy may be necessary, because of the increased chance for multiple additional cancers.⁹

Since 40 to 60 percent of female patients will develop

endometrial cancer, it is recommended that annual screening begin between the ages of 30 to 35 and include endometrial aspiration and transvaginal ultrasound. Prophylactic hysterectomy and oophorectomy should also be strongly considered after childbearing is complete.⁹

Family history is often the key to diagnosing HNPCC. Features of which to take note should include: two or more relatives with an HNPCC-related tumor (i.e. colon, uterine, stomach or ovarian), two or more affected generations, or an individual with an HNPCC-related tumor under the age of 50 or with two synchronous or metachronous tumors. Identifying a family or individual with any one of these features may suggest that a formal evaluation for HNPCC is necessary.

Adenomatous polyposis syndromes

Adenomatous polyposis syndromes are associated with multiple polyps in the colon. Two of these syndromes, familial adenomatous polyposis (FAP) and attenuated familial adenomatous polyposis (AFAP), are dominantly inherited conditions caused by mutations in the adenomatous polyposis coli (APC) gene. A third polyposis syndrome, often referred to as MYH-associated polyposis, is a recessive condition caused by two mutations in the MYH gene.

In classical FAP, individuals develop hundreds to thousands of polyps throughout the colon, usually as a teenager or young adult. The major concern with this condition is that the polyps will become cancerous, and there is nearly a 100 percent chance for malignancy if they are not removed. The polyps often begin to form around age 16. For this reason, prophylactic colectomy is often done between the ages of 16 and 20 to minimize risk for malignancy.⁸

FAP displays variable expressivity, sometimes displaying extracolonic features. Additional manifestations can include desmoid tumors, osteomas, dental anomalies and congenital hypertrophy of the retinal pigment epithelium (CHRPE). If additional features are found in association with multiple polyps, it's possible that a separate overlapping syndrome such as Gardner syndrome or Turcot syndrome may be present.⁸ Gardner syndrome is characterized by colonic polyposis typical of FAP found together with osteomas and soft tissue tumors. Turcot syndrome is the association of colonic polyposis and central nervous system tumors.

In contrast to classical FAP, attenuated FAP (or AFAP) is characterized by fewer colon polyps. It still, however, carries a significant risk for colorectal cancer if polyps are left untreated. Most individuals with AFAP develop 10 to 99 colon polyps. These polyps tend to be found more proximally in the colon than in classic FAP.

When eliciting a family history of a patient with multiple

polyps, emphasis should be placed upon: parents or siblings with multiple colon polyps, the number of generations affected with colon polyps, childhood colon or upper gastrointestinal cancers, and rare tumors (e.g., desmoid tumors). It is also important to note if there is a lack of multiple affected generations, since this could more strongly implicate a recessive form of polyposis.

The two genes most commonly associated with polyposis are APC and MYH. APC is the more common of the two. An identifiable APC gene mutation can be found in more than 90 percent of individuals with classic FAP and in 30 percent of individuals with AFAP. More recently discovered, MYH-associated polyposis is inherited in an autosomal recessive manner. It is believed that 33 percent of individuals who have 15 to 100 polyps and test negative for an APC gene mutation will test positive for two mutations in the MYH gene.¹³

Individuals may wish to consider APC genetic testing if they have had more than 10 polyps during the course of their lifetime or if there is a known mutation in their family. Genetic testing of the MYH gene may be appropriate for families with polyposis who have tested negative for the APC gene, or those who appear to demonstrate an autosomal recessive inheritance pattern.

Medical recommendations for someone who has AFAP or MYH-associated polyposis include colonoscopy every two to three years beginning at age 12 to 20 years and colectomy if more than 20 to 30 adenomas are identified. Esophagogastroduodenoscopy (EGD) should also be done beginning by age 25 years and repeated every one to three years.¹⁴

Familial Colon Cancer

In some instances of colon cancer, a family has more diagnoses than can be explained by random chance, yet the family does not have an identifiable cancer gene mutation. In these circumstances, the colon cancer is said to be familial, and risk to family members must be based on empiric risk estimates and model-based prediction algorithms. It is believed that 20 to 30 percent of all colorectal cancers have a familial basis.¹⁵

Numerous studies have explored the risk of cancer in the context of family history and have consistently found that first-degree relatives of affected individuals are themselves at a twofold to threefold increased risk of colorectal cancer. With no family history of colorectal cancer, there is a 4 percent lifetime risk of developing the disease (by age 79). The risk jumps to 8 to 9 percent with one affected first-degree relative and to 15 percent if that first-degree relative is diagnosed under the age of 45. If an individual has more than one affected first-degree relative (at any age) the risk for colorectal cancer is 16 percent.¹⁶ Additionally, familial

factors also appear to influence the age of onset of colorectal cancer. People who have a first-degree relative with colorectal cancer are estimated to have an average onset of colorectal cancer about 10 years earlier than people with sporadic colorectal cancer.¹⁷

Prostate Cancer

Prostate cancer occurs in approximately one in six men. Of those who develop it, about 20 percent will die from the disease. In many cases, however, prostate tumors grow slowly. If the cancer is detected early, five-year survival rates in South Dakota approach 100 percent.¹⁸

Risk for prostate cancer, as well as its progression, can be influenced by many factors, including race, diet, sexual activity, age and family history.¹⁹ African-American men tend to have the highest risk, while Asian men appear to have the lowest risk. Also, men who eat a lot of red meat or high-fat dairy products appear to have a slightly higher chance of getting prostate cancer. Of all risk factors, however, age plays the biggest role. For example, only one in 45 men are diagnosed under age 59, while the risk is one in seven for men ages 60 to 79.²⁰

After age, family history is the next strongest risk factor for prostate cancer. Risk increases with both the number of diagnoses in a family as well as with any diagnoses that occur at younger ages. If a male has a brother with prostate cancer, his risk is three times greater than the general population to also develop prostate cancer. If an individual has two first-degree relatives diagnosed at any age, the risk increases to five times the background risk.²¹ Furthermore, some studies have demonstrated that men have an increased risk for prostate cancer if their mother or sister have had breast or ovarian cancer.²²

The genetics of prostate cancer have proven challenging. With the exception of BRCA, which likely only accounts for 5 percent of all familial and early onset prostate cancer, no single genes have emerged as hereditary cancer predisposition genes for prostate cancer. Twin studies, nevertheless, have determined that 42 percent of prostate cancer risk may be accounted for by heritable factors and numerous other studies have concluded that much of the risk is due to highly penetrant autosomal dominant genes.²²

While specific single genes for familial or hereditary prostate cancer have not been implicated, there are many genes that have been reported as possible candidate genes. Some of these include CHEK2, ELAC2, HSD17B3 and RNASEL. There are now laboratories testing for a number of these genes, but the current dilemma with such testing is that the risk conferred by each of these genes is not known, so meaningful interpretation is not available. In fact, each gene tested only accounts for a small fraction of the overall familial risk. As an example, CHEK2 mutations are only

seen in 4 percent of all prostate cancers.²³

While various studies have suggested that a single gene mutation is the mostly likely cause of inherited prostate cancer, the fact that no single gene has been discovered leaves open the possibility of multifactorial inheritance. In other words, it is possible that there are many genes, plus environmental factors, working in combination to influence the risk for prostate cancer.

As of yet, there have not been quality studies which have determined the most appropriate screening and surveillance strategies for men with a familial/inherited risk for prostate cancer. Although the optimal timing has not been studied, the age of 40 has been suggested as the most appropriate age at which time men with increased risk should be offered PSA testing. Even though there are no clear recommendations, all men with a family history of prostate cancer should be offered genetic counseling to review family history.

Genetic counseling can help in identifying families with hereditary prostate cancer. Obtaining and analyzing a family history may determine the mode of inheritance which could help facilitate genetic testing for some. Families with three or more first-degree relatives with prostate cancer, families with three successive affected generations (either maternal or paternal), or families with two relatives under the age of 55 should be considered for referral.²¹ One study in particular surveyed sons of men with prostate cancer and found that 90 percent wanted to know if they were at increased risk and indicated they were likely to undergo increased screening or consider genetic testing.²⁴

Lung

Since smoking is undeniably the number one factor influencing the risk to develop lung cancer, it can be easy to overlook other factors. One factor that shouldn't be overlooked, however, is family history. An underlying genetic susceptibility to lung cancer has been suggested by numerous studies showing familial trends even after adjusting for family smoking habits.²⁵ These studies have suggested that smokers who have a first-degree relative with early-onset lung cancer have a lifetime risk of between 17 percent to 25 percent to develop lung cancer.²⁶

In the clinical setting, family members of individuals diagnosed with lung cancer usually recognize the influence of smoking but often do not realize the role that an inherited predisposition to lung cancer may play. Family members should be made aware that first-degree relatives of patients with all forms of lung carcinoma are at a two to three-and-a-half-fold increased risk compared to the general population, and that the risk for second- and third-degree relatives is also increased.²⁷

Lung cancer is a multifactorial genetic condition, with both

environmental and genetic factors influencing its development. Although the environmental components of lung cancer are extrinsically apparent, the genetic factors leading to lung cancer have proven much more difficult to study. A 2009 study, however, has strongly implicated a gene known as RGS17 as a candidate for lung cancer susceptibility.²⁸ This gene is found on the q arm of chromosome No. 6. RGS17 has been found to be highly expressed in tumor tissues. To date, clinical testing for RGS17 is not available and a search for other candidate genes and modifier genes remains underway.

Genetic Counseling, Genetic Testing, and Risk Assessment

Cancer genetic counseling is a process whereby complex genetic information is translated to patients in an easily understood way, typically by master's level genetic counselors. The goal of cancer genetic counseling is to provide clear and clinically important information about genetic risk factors. Genetic counselors educate patients about their chance of developing cancer, help them derive personal meaning from cancer genetic information, and empower them to make educated, informed decisions about genetic testing, cancer screening and cancer prevention.⁶ The information presented during genetic counseling may help in the prevention or early detection of hereditary cancer. Alternatively, in our personal experience, many patients find out their risk to develop cancer is much less than what they anticipated and appear reassured by the information presented.

During any genetic counseling session, a detailed family history/pedigree is collected. Eliciting and analyzing a genetic pedigree is the foundation of cancer genetic risk assessment. By analyzing the family history, the genetic counselor is able to establish the likelihood of an inherited cancer syndrome, conclude if genetic testing is appropriate and determine the risk for cancer (or cancer recurrence). In addition to this individual multifaceted cancer risk assessment, other core components of cancer genetic counseling include education, counseling and the establishment of a cancer risk management plan. It is also necessary to ascertain what the level of risk means to each individual patient and to get them to contemplate how they will act upon this risk.²⁹

A referral for cancer genetic counseling should be considered for those patients with personal or family history features suggestive of familial or hereditary cancer and should not be limited to just those individuals who are potential candidates for genetic testing. Individuals from high risk families may benefit from a detailed discussion about the heritability of cancer in their families and appropriate cancer risk management strategies. Genetic counseling does not always require genetic testing and, in fact, the majority of men or women who meet with a

genetic counselor do not have a test performed.

In some families, there is more cancer than one would expect by chance alone, yet the family doesn't fit a clear a pattern of inheritance and usually does not have a single gene mutation causing the cancers. In these families, the cancer is said to be familial. Currently, sophisticated models are available to help estimate lifetime cancer risks for familial cancer.³ By taking into account those family members who have had cancer, as well as those who have not, lifetime cancer risk estimates can be calculated and discussed with the patient. While those with familial cancer may not benefit from genetic testing, they do benefit from genetic counseling as a way to understand and act upon such risks.

Finally, risk estimates themselves are not static since family histories tend to be dynamic. Because of this, it is important that patients take note of and report new cancer diagnoses or other pertinent family health history that occurs after an initial genetic risk assessment. The occurrence of additional cancers in a family after someone has initially met with a genetic counselor may alter the likelihood of a cancer predisposition gene or change empiric cancer risk estimates. Moreover, as family histories are not static, neither is genetic discovery and new genes will continue to be discovered following the primary genetic consultation. Medical surveillance and treatment options for cancer will continue to evolve as new genes continue to be discovered.

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