Cancer and Genetic Medicine

The Third Pair of Articles in a Series about the Significance of Genetic Science for Catholic Health Care

A MEDICAL VIEW

BY JEFFREY G. SHAW

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Approximately one in three Americans will develop a malignancy at some time in his or her life. One in four deaths in the United States is due to cancer. Cancer is second to heart disease as the most common cause of death in the nation. Needless to say, cancer has an enormous impact on the lives of millions of people and on the medical system that takes care of these people.

Cancer is caused by mutations in a variety of genes responsible for controlling the growth of cells, either directly or indirectly. All cancer is "genetic" in the sense that cancer is the uncontrolled division of a cell and the genes control cell division. At the molecular level, therefore, all cancer is due to mutation (a change in the genetic code) in our genes. These mutations are usually caused by decades of exposure to carcinogens, which damage genes (see **Figure**).

With the completion of the Human Genome Project (HGP), identification of genes has progressed at an exponential rate, including identification of the genes responsible for the control of cells. As a result of this new understanding of the basic abnormalities that lead to cancer, the medical field called oncology will drastically change over the next decade.

Cancer Basics

To understand how the genetic revolution will transform the treatment of cancer, we need to review the basics of how cancer occurs. What is the difference between normal cells and cancerous cells?

Normal cells:

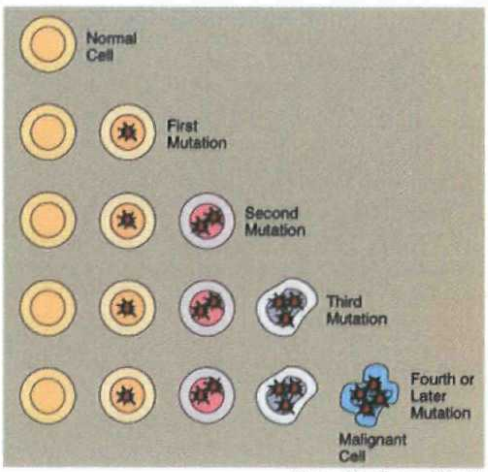
- Reproduce in an organized, controlled, and orderly manner
- Do not divide when space or nutrients are inadequate
- Do not spread into parts of the body where they do not belong
- Become fully differentiated to perform specific tasks
- Have limited potential to replicate, over time lose their ability to do so, and eventually die

Cancerous cells, on the other hand:

- Have uncontrolled cell growth, even when space and nutrients are lacking
- Have the ability to initiate new growth at distant sites
- Can become poorly differentiated, eventually looking different from the cells where they originated

Figure

Gene Mutations



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• Can escape detection and destruction by the immune system

We've said that most cancers are the result of genetic mutations caused by exposure to "carcinogens." A carcinogen is any substance, situation, or exposure that can damage genetic material (DNA). The hundreds of known carcinogens include factors such as metabolic processes (e.g., free radicals, hormones), viruses (e.g., hepatitis B, human papilloma virus), chemicals (e.g., tobacco, alcohol, asbestos, heavy metals), and radiation (e.g., radiation therapy, ultraviolet light, radioactive materials).

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Genes and Cancer

Hundreds of genes have been identified as directly or indirectly participating in a cell's ability to control growth. Given the success of the HGP, this list of genes is sure to get longer. At present, genes controlling cell growth are divided into four major categories: oncogenes, tumor suppressor genes, mismatch repair genes, and "housekeeping" genes.

• *Oncogenes* result from an acquired mutation in normal genes called "proto-oncogenes." The role of the proto-oncogenes is the signaling of a cell to divide. Normal cells replicate to replace damaged or dying cells. "Activation" describes the mutation in a proto-oncogene that transforms it into an oncogene. These mutations push the cell to divide when it is not supposed to. Therefore, the mutation of one proto-oncogene of a particular pair (most genes occur in identical pairs, one from the mother and one from the father) can lead to the initiation of cancer. Examples of oncogenes are abl, myc, ras, and ret. (For a discussion of genetic "language," see Jeffrey G. Shaw, "An Introduction to Genetics," *Health Progress,* May-June 2005, pp. 47-48.)

• *Tumor suppressor genes* actually have a variety of functions in the control of a cell's growth. They are growth suppressing, playing an important role in the regulation of cell growth, either directly or indirectly. One can consider a tumor suppressor gene the opposite of an oncogene. If just one copy of a particular tumor suppressor gene (either maternal or paternal) is working in a cell, it will be sufficient to control cell growth. But loss of function of both the maternal and paternal copy of the gene can lead to unregulated cell growth. Examples of tumor suppressor genes are BRCA1, BRCA2, APC, and WT1.

• *Mismatch Repair Genes* Every time a cell replicates and divides, all three billion letters of genetic code must be duplicated perfectly to create a new cell—a daunting task. Unfortunately, errors are made, and these need to be corrected. Mismatch repair genes perform this function. They act like "spell-checkers," automatically correcting mistakes. Damage to both pairs of a mismatch repair gene will result in a loss of function, and the cell will accordingly build up mutations every time it divides. Over time, proto-oncogenes, tumor suppressor genes, and other genes involved in cell growth can be damaged and cancer can occur. Examples of mismatch repair genes are MLH1 and MSH2.

• *Housekeeping Genes* are difficult to summarize. There are hundreds of housekeeping genes, and researchers are just beginning to identify their roles. In general, housekeeping genes keep the cell clean and functional. For example, housekeeping genes break down carcinogens that enter a cell, regulate estrogen in the cell, and protect against viral activation of cancer in the cervix. These genes generally do not participate directly in cell growth regulation. Instead, their function seems to be directed toward protection of the cell from carcinogenic invaders or processes.

Cancer Risks

Everyone has a "general population risk"—a risk level based on the occurrence of cancer in a given population—to develop a type of cancer. The risk level can be increased or decreased, depending on a person's environmental exposures and lifestyle. For example, a person who uses tobacco products increases his or her risk level for lung, throat, colon, and many other types of cancer over the risk level of the general population. People with significant exposure to ultraviolet light (from sunlight or tanning beds, for example) have an increased risk for skin cancers.

Given the complexity of environments, reproductive decisions, physical development, occupations, and differing lifestyles, it is unlikely that any one person would have a general population risk for all types of cancer. A person's risk for a specific type of cancer can be determined as falling into one of three general categories.

Sporadic Most cancer occurs in a sporadic pattern. Because the patient has no family history for it, the disease appears to have "come out of nowhere." In such cases, the tumor suppressor, mismatch repair, and other important genes inherited from parents are fully functional at birth. The cancer is caused primarily by multiple exposures to carcinogens. Sporadic cancers—breast, colon, prostate, and ovarian cancer are examples—tend to occur later in life, usually after age 50. By that time, the person is likely to have accumulated many mutations, and his or her immune system is likely to be less proficient in protecting against cancer cells. However, sporadic cancers also occur in childhood or youth (i.e., testicular cancer).

Inherited In cases involving an inherited (sometimes called a "high penetrance") cancer predisposition, the person has inherited a faulty tumor suppressor, oncogene, or mismatch repair gene from a parent. Because the mutated (nonfunctional) gene was present in the egg or sperm, it is present in every cell of the body. Some sort of environmental insult will be necessary to mutate the other gene of the pair sufficiently to initiate the possibility of cancer. But because of the inherited mutation, the person will have a significant increase in risk for malignancy, usually in specific organs.

The cancer in such cases often has an early onset, and the risk for second primary tumors is increased significantly. Inherited cancer predispositions do not "dilute." Either a child inherits the faulty gene from a parent and has a significantly increased risk for cancer, or the child does *not* inherit the faulty gene and does not have an increased risk (depending on the family history of cancer).

For example, people with an inherited predisposition, because of an inherited mutation in either the BRCA1 or BRCA2 tumor suppressor genes, will have a 44 to 85 percent lifetime risk of developing the disease, instead of a normal risk of about 10 percent. And people with a high risk will also have a 50 percent chance of developing the disease before age 50, instead of the usual 2 percent risk. Their risk for developing a brand new breast cancer will run as high as 60 percent, as will their risk for a primary ovarian cancer.

Familial In familial (sometimes called "multifactorial low penetrance") cancer predispositions, the person involved has inherited several housekeeping genes that, although functional, are not doing a good job of protecting the patient from carcinogens. Affected families usually have an excess of cancer cases, but the illness does not necessarily occur in youth. The cancer toward which the family is predisposed need not be genetically related. (For instance, the tumor suppressor genes controlling the growth of cervical cells differ from those controlling breast cells; breast and cervical cancer, for example, are not genetically related).

Familial predispositions are "multifactorial" conditions. In other words, the patient involved must inherit several suboptimal housekeeping genes and be exposed to specific carcinogens. As a result, familial predispositions tend to "dilute" over each generation because it is difficult to pass down several specific genes, and families are usually not exposed to the same environmental conditions over several generations. Therefore, familial predispositions tend to confer a small to moderate increase in the risk for cancer.

Familial predispositions tend to "dilute" over each passing generation.

Impact on Medical Care

We are today experiencing an explosive growth of knowledge regarding basic alterations of cells that lead to cancer. This knowledge has begun a process that will vastly change the medical management of cancer patients.

Diagnosis/Prognosis The specific characterization of the genetic damage that has occurred in a tumor will provide physicians with a more clearly defined understanding of the tumor's aggressiveness, as well as help them predict risk for metastasis (spread of a cancer to other parts of the body) and survival.

Testing breast tumors for overexpression of the gene Her2-neu is now commonplace. Women with increased expression of this gene are known to have more aggressive cancers. Identification of this abnormality has led to development of a new drug called Herceptin, which blocks the Her2-neu protein and improves the patient's chances for survival.

New tumor multigene analysis is today helping stage I breast cancer patients determine whether their risk of recurrence is high or low. For example, a woman might be diagnosed (on the basis of tumor size, lymph node involvement, and other

signs) as having an early-stage breast cancer, which would ordinarily indicate a relatively low chance of recurrence. Suppose, however, that multigene analysis shows a genetic "footprint" of the tumor indicating a much higher chance of recurrence. The woman could then opt for more aggressive management of her initial tumor, thereby reducing the risk of recurrence. By the same token, multigene analysis showing a low chance of recurrence could help prevent overtreatment.

Recent research performed by Mingxin Che, MD, PhD, at Wayne State University, Detroit, is likely to help patients with prostate cancer.[1] Che and his colleagues evaluated the expression of the P53 oncogene in the tumors of prostate patients. P53 is a well-known oncogene that, when activated, promotes tumor growth. Studies done by Che and his colleagues showed that men having prostate tumors with abnormally high levels of the P53 protein were twice as likely to develop distant metastases at five years and had a higher than normal mortality rate.

Pharmacogenetics The tailoring of drugs for patients whose individual response can be predicted by gene expression profiles, or "fingerprinting" of the tumor, can help identify those likely to benefit from a specific treatment and those not likely to benefit. For example, "fingerprinting" a tumor can indicate which form of chemotherapy is likely to produce the fewest side effects in the patient and improve his or her prognosis.

Tumor "fingerprinting" of this kind has been helpful in showing why standard therapies for acute lymphoblastic leukemia cure 80 percent of children afflicted by the disease, even though the same drug therapy fails the other 20 percent. Research done late last year by Pier Paolo Pandolfi, MD, PhD, indicated that young patients with a working PTEN gene in their tumors are more responsive than others to the drug Herceptin.[2]

About 10 percent of patients with chemotherapy-resistant colon cancer respond to two different monoclonal antibodies. These drugs target the epidermal growth factor receptor (EGFR). Current studies show that testing of the EFGR gene can help identify people who will benefit from these therapies. By the same token, the test also identifies those who, because they won't benefit from the medication, should not be exposed it.

Therapy and Risk Prediction

Currently, most cancer therapeutics operate according to a single paradigm: They damage DNA in rapidly dividing cancer cells, thereby killing those cells. In the case of chemotherapeutic treatments, this is not an ideal way to target a cell, because many noncancerous cells of the body also divide rapidly—for example, hair cells and the cells lining the gastrointestinal tract. As medical science increases its genetic understanding of the ways cancer occurs, it will develop new ways to attack a tumor. Comprehension of a tumor's genetic nature has already led to the development of Gleevec, for gastrointestinal tumors and one type of leukemia, and Herceptin, for some types of breast cancer. Targeted therapies will be developed (and improved) for other kinds of cancer.

As for predicting cancer risks, presymptomatic genetic testing is currently available for a number of inherited cancer predispositions. In families with histories suggesting an inherited predisposition, such testing can show which family members have a high risk for developing cancer and which do not. No special intervention would be necessary for those determined not to have an increased risk. For those found to have an increased risk, surgical or chemotherapeutic intervention can drastically reduce the risk for cancer. Furthermore, screening techniques for people at risk can be altered to help detect a possible cancer at the earliest stage, when it will be most amenable to treatment.

However, highly penetrant, inherited cancer predispositions account for only a small proportion of all cancer occurrences. Medical science must expand testing to cover the more common, lower-penetrated cancer predispositions. A recent study indicates that people with a common specific variant in the CASP8 gene (a gene involved with programmed cell death) have an approximately 40 percent *lower* risk of developing breast cancer than people with a different variant.[3] Given improved understanding of the gene variants that protect us from cancer, we will be able to test greater numbers of people to determine whether they are at an increased or decreased risk for cancer.

Oncology and the Future

Knowledge about the fundamental changes in cell genes that lead to cancer is sure to greatly affect risk assessment, diagnosis, and treatment. These advances will significantly alter the practice

of medical oncology. Identification of people with inherited or familial risks for cancer will show us those who are likely to benefit from preventive interventions, including screening to identify tumors at an early stage.

Advances in genomic technology will improve our ability to predict when a tumor is likely to metastasize to other parts of the body—and when the patient might, accordingly, benefit from a more aggressive therapy. It will aid us in understanding which types of treatments will be beneficial to a specific patient and which will not.

New biologic therapeutic treatments for cancer promise to be more effective—and to have fewer toxic side effects—than currently available treatments. The biggest challenge will likely be incorporating this wealth of new information into clinical practice. ■

NOTES

1. M. Che, M. DeSilvio, A. Pollack, et al., "Prognostic Value of Abnormal P53 Expression in Locally Advanced Prostate Cancer Treated with Androgen Deprivation and Radiotherapy: A Study Based on RTOG 9202" (paper presented at the American Society of Clinical Oncology's 2005 Prostate Cancer Symposium, Orlando, FL, February 19, 2005); abstract at www.asco.org/ac/1,1003_12-002643-00_18-0037-00_19-0020372,00.asp.
2. P. P. Pandolfi, "Breast Cancer—Loss of PTEN Often Predicts Resistance to Treatment," *New England Journal of Medicine*, November 25, 2004, pp. 2,337-2,338.
3. G. MacPherson, C. S. Healey, M. D. Teare, et al., "Association of a Common Variant of the CASP8 Gene with a Reduced Risk of Breast Cancer," *Journal of the National Cancer Institute*, vol. 96, no. 24, December 15, 2004, pp. 1,866-1,869.

AN ETHICAL VIEW

BY CAROL BAYLEY, PhD

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Jeffrey Shaw's introduction to cancer genetics (p. 31) describes a future in which advances in genomics make possible new diagnostic tools and therapeutic agents and vectors. But the ethical issues it raises are familiar ones, even if set into a new context. What is the right relationship between efforts to improve individuals' health and efforts to improve the health of a population as a whole? How will physicians learn the skills needed to educate patients in a way that secures truly informed consent? How will insurance plans fairly meet their obligations to their shareholders to circumvent avoidable risk, as well as their obligations to those they insure to help them escape financial disaster if they get sick? Many of these questions puzzle us right now. But let's look at how the same questions may puzzle us in new ways in light of Shaw's descriptions.

Old Issues, New Questions

Someone famous said, "To a hammer, the world looks like a nail." When you have only one solution, the temptation is to frame every problem as one amenable to that solution. The hammer here is genetic testing, and the information it may yield about an individual's cancer risk. The temptation may be to focus attention and direct resources to risk identification and reduction in certain individuals at the expense of attention and resources that might be devoted to environmental contributions to cancer risk. These latter interventions may be larger, slower, and more diffuse opportunities. But, as Shaw points out, most cancers are sporadic (not inherited) and most genetic mutations result from repeated exposures to carcinogens in the environment. At a time when resources are limited, we should carefully consider whether individual or population screening for certain cancers is a better or worse use of our money than is cleaning up our air and water, or figuring out politically and economically workable solutions to industrial wastes that we already know contribute to cancer.

Of course, the challenge here is to configure our finances and accounting so that the relationship Shaw describes between environmental carcinogenic exposure and increased cancer risk is clearer, in economic terms, than it is at present. Otherwise, we will continue to hit the nail of cancer with the only hammer we have.

Another old ethical issue in new genetics clothing is that of informed consent. This issue has at least two facets. First, as Shaw points out, we are beginning to differentiate cancers not just on the basis of where in the body they occur, or by cell

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