

The Environment, Genes, and Cancer

Statement

of

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Good morning. I am Deborah Winn, Ph.D., Acting Associate Director, Epidemiology and Genetics Research Program, National Cancer Institute (NCI). Thank you, Senator Clinton and distinguished Members of the Committee, for inviting me to talk with you about NCI research on cancer, genes, and the environment. Conceptual and technical breakthroughs and the often breathtaking pace of scientific discovery have engendered among cancer researchers a tremendous sense of optimism that new avenues will be found to prevent, detect, diagnose, and treat cancer. Nowhere is the sense of promise greater or the potential more profound than at the interface of epidemiology and genetics. By marrying the study of the distribution and causes of cancer in human populations with cutting-edge genetic and related molecular technologies, we will, over time, be able to design new approaches to health and cancer care based on an understanding of how genes modify and interact with environmental exposures.

The Environment, Genes, and Cancer

The term "environment" refers not only to air, water, and soil, but also to substances and conditions in the home and workplace. It includes dietary components; the use of tobacco, alcohol, or drugs; exposure to chemicals, and sunlight and other forms of radiation; and infectious agents. Lifestyle, economic, and behavioral factors are all aspects of our environment. To date, we know that tobacco is the environmental exposure most significant to the cancer burden. Factors that are absent from our environment, as well as those that are present, influence our cancer risk.

Cancer susceptibility is another critical piece of the puzzle. For example, why does one person with a cancer-causing exposure develop cancer, while another does not? Genes may be the key. We know that disruption of fundamental cellular processes contributes to the development and progression of the more common, non-hereditary forms of cancer.

Yet even among individuals who have inherited cancer-predisposing genes, the risk of developing cancer appears to be modified by other genetic and environmental factors. There is mounting evidence that a person's genetic make-up may influence susceptibility or even resistance to cancer-causing exposures.

Some cancers are associated with defects in one or a few genes. An example is the Li-Fraumeni syndrome, which involves an inherited tumor suppressor gene and is associated with familial occurrences of breast cancer and certain other cancers. However, most cancers involve many genes. Individuals may inherit defects in these genes, or they may experience environmental exposures or other circumstances that cause gene mutations, which are changes in gene structure. Most mutations do not affect the normal processes of cells in which they occur; but if alterations occur in genes that control such functions as metabolism of carcinogens, DNA repair, metabolism of nutrients, hormones and other factors, cell cycle control factors, or immune function, among others, cellular processes may become abnormal. Cancer arises through the accumulation of multiple mutations in genes resulting from multiple exposures over a period of years or decades.

Understanding the interaction of genes with other genes and environmental factors in the development of cancer is critical. Gene-environment interactions are evident when the risk from an environmental exposure varies depending on individual genetic make-up. For example, the CYP family of genes controls metabolism of some carcinogens. Each of us has CYP genes, but the exact structure of the genes varies from person to person. People with specific variants face a higher risk, by two to ten fold, of developing tobacco-related cancers such as lung cancer, esophageal cancer, and cancer of the oral cavity, than those individuals who have other CYP gene variants. This risk increases as the level of exposure to tobacco smoke increases. Furthermore, certain combinations of CYP variants, and variants of another gene, GSMT1, interact, resulting in even greater risks of these cancers.

NCI Approach to the Study of Gene-Environment Interactions

The NCI has greatly expanded its efforts to identify the genetic and environmental risk factors leading to cancer susceptibility in individuals, families, and populations; evaluate the interactions of these risk factors; assess the relevance of these risk factors to clinical practice and public health; and address the diverse and complex scientific, ethical, legal, and social issues associated with this research. The NCI has identified the study of genes and the environment as a high priority research area with great potential for discovery. As our knowledge base expands in this critical area, we will be able to quantify the cancer risks associated with specific environmental and genetic factors and their interactions, and design new approaches to health and cancer care based on an understanding of how genes modify and interact with environmental exposures.

NCI's investment in the study of genetics has yielded enormous dividends. For example, NCI's Cancer Genome Anatomy Project has resulted in the discovery of approximately 40,000 new genes. New technologies have permitted scientists to determine which genes are active in normal or in cancerous tissues. There has been an exponential increase in the

pace of identifying genes that maintain the integrity of our genetic material, regulate cell growth and development, and determine our response to hormones and other chemicals produced by the body or in the environment. Related discoveries have enabled us to characterize the function of hundreds of new genes and pathways. Vast public databases contain millions of entries describing gene sequences and their location in the human genome.

NCI has expanded the tools available to the cancer genetics research community through the World Wide Web. Through the Genetic Annotation Initiative of the Cancer Genome Anatomy Project, scientists have identified more than 20,000 genetic variations, and they expect to expand that number to nearly 500,000 by 2002. Researchers are using sophisticated computer programs to identify variations in specific genes in people with cancer to determine which variants are associated with certain types of cancer and whether some variants occur more often in some populations. New technology development through the Innovative Molecular Analysis Technologies Program is also improving our ability to effectively analyze the large volumes of samples and data in these population-based studies.

Members of the Mouse Models of Human Cancers Consortium (MMHCC) are developing and validating mouse models - mice with cancers similar to the major human cancers that can be inherited. These models will be made available to scientists for research. Composed of 20 groups of investigators from institutions across the country, the MMHCC uses Web-based discussion forums and other communication tools to integrate emerging knowledge about cancer susceptibility from animal models with studies on human populations. The MMHCC also supports a repository for models of key cancers caused by specific gene variants.

We have gained tremendous insight into risks for cancer by examining the personal and medical histories of high-risk families and investigating how cancer-predisposing genes are modified by other genes and environmental factors in these families. For example, through the Cooperative Family Registries for breast/ovarian and colorectal cancers, we have collected clinical, epidemiological, and pathological data as well as biospecimens for over 8,000 high-risk families. Analysis of this information may lead to targeted approaches for the prevention, detection, and diagnosis of cancer.

Establishing significant and valid evidence for gene-environment interactions requires studies of large populations over long periods of time. In cohort studies, information on exposures to factors that might affect cancer risk and biologic samples are collected from individuals in large population subgroups. By systematically following these people over time to determine who develops cancer and who remains cancer free, scientists can understand the risk of developing cancer for those with specified exposures and genetic profiles. In this way, early detection can be directed to those at greatest risk, and diagnosis and treatment can be tailored to individual needs. NCI is establishing a Cohort Consortium of investigators from around the world to facilitate the pooling of data on very large numbers of people, foster collaborative links among resources, and organize collaborative studies. Another type of large population study is case-control studies,

which retrospectively examine exposure histories and genetic profiles of people who already have cancer (cases) and compare them with those of people who have not developed cancer (controls). NCI is assembling a Case-Control Consortium to support large-scale studies of gene-environment interactions for less common cancers.

Long Island Breast Cancer Study Project

One illustration of NCI's approach to the investigation of the relationship between genes and the environment in the development of cancer is the Long Island Breast Cancer Study Project (LIBCSP): a multistudy research initiative examining the possible role of environmental factors in breast cancer in Suffolk, Nassau, and Schoharie counties in New York and Tolland County, Connecticut, where rates of breast cancer incidence are elevated. The LIBCSP used a full array of scientific approaches to study breast cancer on Long Island, and consisted of more than 10 studies that include human population (epidemiologic) studies, the establishment of a family registry for breast and ovarian cancer, and laboratory research on mechanisms of action and susceptibility in breast cancer development.

Originally conceived as part of the LIBCSP, a new tool has been created by NCI to help overcome the frustrations associated with studying geographic variations of disease: a prototype computer system called the Geographic Information System for Health (GIS-H). The GIS-H allows examination and tracking, over time and space, of cancer rates with any geographically defined factor that might contribute to the cancer burden. It is the largest and most comprehensive system of its type developed for the study of breast cancer. The GIS-H is a new approach for researchers to use in investigating relationships between breast cancer and the environment, and to estimate exposures to environmental contamination. The GIS-H data layers will include geographic data for precise mapping and geographic location of features in all data layers. Demographic data on health care facilities, health care surveys, breast cancer, and the environment will also be included. The environmental data will include information on contaminated drinking water; sources of indoor and ambient air pollution, including emissions from aircraft; electromagnetic fields; pesticides and other toxic chemicals; hazardous and municipal waste; and radiation. The system will rely chiefly on existing databases obtained from federal, state, and local governments, and private sources - including historical information on environmental exposures from residents - with emphasis placed on high-quality data. More than 80 databases are slated to be included in the system. The GIS-H provides the opportunity to apply a powerful emerging technology to the study of environmental causes of breast cancer and is anticipated to be ready for investigator-initiated pilot studies this year.

Atlas of Cancer Mortality

Because geographic patterns of cancer may provide important clues to the causes of cancer, the NCI has, for over 30 years, studied geographic patterns of cancer mortality across the United States. Our most recent effort in this area is an updated atlas of cancer mortality. The new *Atlas of Cancer Mortality in the United States, 1950 - 1994*, prepared

and published by the NCI, is a book and website of maps, text, tables, and figures showing the geographic patterns of cancer death rates throughout the United States for more than 40 cancers, and features 254 color-coded maps that show the geographic variations during 1970-94 compared to those during 1950-69. The color maps make it easy to pinpoint geographic areas with average, below average, or elevated rates. The Atlas, and related information, can be explored at ["/atlasplus/](#). The website allows the user to tailor the data interactively, to produce maps by race, gender, time period, age group, state, state economic area, or county level; and to develop bar charts and trend line graphs. The site also provides links to related sites. The Atlas has been designed so it is accessible not only to researchers, but to the public, consumer advocates, and everyone who is working to improve public health.

The Atlas does not provide information about why death rates may be higher in certain localities than in others, but it can generate leads for in-depth epidemiologic studies that may shed light on factors contributing to cancer risks. Possible risk factors include tobacco use, occupational exposures, dietary habits, ethnic background, and environmental exposures from the air or water. In addition, geographic differences in mortality rates may reflect differences in access to medical care, such as screening, diagnosis, or treatment. We anticipate that many of the leads provided by the new Atlas will guide further epidemiologic and public health activities aimed at preventing cancer.

The NCI is encouraging research proposals for new interdisciplinary studies that use the GIS-H and the *Atlas of Cancer Mortality* to explore geographic variations of cancer incidence and mortality and speed the process of scientific discovery and application. To date, about 30 applications have been received in response to this new initiative.

New Research Directions

Now, more than ever before, opportunities exist to determine how variations in genes combine with environmental and other factors to induce cancer. NCI has identified key priority areas for research on genes, the environment, and cancer, and designed a strategy to capitalize on the opportunities before us. We intend to focus expanded effort on identifying and characterizing gene variations involved in molecular pathways important in cancer development, and new environmental risk factors - and determining their interactions in cancer causation. We are planning initiatives that will develop new ways to assess and measure environmental exposures for use in population studies; develop new experimental models that parallel human cancer-related genes, pathways, and processes; and identify cancer-predisposing genes in high-risk families and investigate how expression of these genes is modified by other genes and environmental factors.

New insights into genetic susceptibility, environmental carcinogens, and their potential interactions can be incorporated into cancer risk prediction models that can in turn be used to estimate individual risk. We now want to refine cancer risk prediction methods and models to integrate genetic and environmental determinants of cancer.

Clinical trials involving genetically high-risk individuals can increase our understanding of the clinical, behavioral, and societal issues associated with cancer susceptibility. We plan to expand enrollment of genetically high-risk individuals into clinical protocols and conduct studies to address the clinical, behavioral, and societal issues associated with cancer susceptibilities.

Conclusion

More than two hundred years ago, as our ancestors abandoned the theory that cancer was the result of an imbalance of bodily humors, scientists first observed that cancer could be linked directly to an environmental agent. As the 21st century dawns, scientific discovery is occurring at a pace that would have astounded our forebears. We have known for a long time that our environment, including our lifestyle choices and economic circumstances, influences our risk for developing cancer; but we have not understood exactly how, or why some people are more susceptible to these influences than others. Over the past decade, there has been an explosion of information on the fundamental nature of cancer, and with the rapid development of dazzling new technologies and tools, we grow closer every day to solving these mysteries that have long confounded us. Success is within our grasp. So, while the questions are complex and our progress has been hard-won, our hope is strong and our dedication is unwavering for a simple reason that each of us here today understands: our goal is to eradicate cancer and save the lives of those who would otherwise be lost to us.

Thank you for this opportunity to tell you about NCI's work. I would be pleased to answer any questions you may have.