Genes and the Environment

Cancer is a complex disease that develops when errors occur in a person's genes. Some of these genetic errors are inherited. Others result from certain environmental exposures or individual behaviors, usually coupled with inherited susceptibility. Through the use of increasingly sophisticated molecular technologies and the tremendous resource generated by the mapping of the human genome, scientists now know that some inherited genetic errors nearly always give rise to cancer, regardless of a patient's environmental or lifestyle history. For example, carriers of mutations in the gene for familial adenomatous polyposis are almost certain to develop colon cancer. Other mutations present at birth only lead to cancer in combination with certain environmental exposures. This relationship is seen in women with *BRACA* mutations, who are at increased risk for hormonally induced breast cancers. Still other cancers are caused by long-term damage to multiple genes caused by environmental factors, with some people inherently at higher risk than others. For instance, people with certain combinations of genetic mutations to the *NAT2* gene are at increased risk for smoking-related bladder cancer.

Scientists have developed technologies to compare complex profiles of genes and proteins from cancer patients to corresponding profiles of cancer-free individuals. This innovation is helping to identify specific molecular profiles associated with cancer risk.

New tools and technologies are helping us to better assess who is at risk for specific cancers based on genetic makeup and environmental exposures. Furthermore, we are increasingly able to identify and assess a variety of carcinogenic exposures encountered outdoors, in the home, and in the workplace. These include pollutants in air, water, and soil; components of food, tobacco, alcohol, and drugs; sunlight and other forms of radiation; and infectious agents. Other new technologies are revealing the intricate biological processes involved in the development of cancer.

To build on this progress, NCI must continue to develop novel ways to study the complexities of genetic and environmental contributions to cancer. We must support both individual efforts and large collaborative programs to maximize the availability of population data, biospecimens, laboratory models, and *in vitro* observations. In particular, large-scale studies with new levels of interdisciplinary cooperation and innovation are needed. These investments will help scientists uncover environmental risk factors, identify genetically susceptible individuals, develop appropriate interventions and precautions for people at high risk, and generate new individual and public health strategies to avoid adverse exposures.

PROGRESS IN PURSUIT OF OUR GOAL

Discovery

NCI is pursuing research opportunities in several growth areas to better understand cancer-related genes, environmental and lifestyle factors, and their interactions.

Building Capacity through Large-Scale Collaborations

NCI continues to promote collaboration through **cohort consortia**, bringing together researchers across the United States and Europe who are studying the same disease site to collaborate and pool exposure data and biospecimens. This type of data pooling is essential for detecting patterns. The Cohort Consortium for Breast and Prostate Cancer pioneered the approach and developed the Hormone-Related Gene Variants program to identify genes that may influence a person's susceptibility to hormone-related breast or prostate cancer and to develop methods of data sharing across genome and genotyping centers, removing a major obstacle to consortium research.

NCI also supports development of **case-control consortia** composed of epidemiologic investigators studying less common cancers. For example, the InterLymph Consortium is studying the genetic and environmental basis of non-Hodgkin's lymphoma. Another consortium is focusing on brain tumors. Members of the NCI-supported Health Maintenance Organization Cancer Research Network are pooling their resources to develop the largest ever case-control study of pancreatic cancer. In addition, we are examining the feasibility of a cohort study in India to focus on nutrition and gene-diet interactions in cancer causation.

NCI and NIEHS collaborations encourage the development and use of innovative methods for assessing difficult to measure environmental exposures.

Assessing and Measuring Environmental Exposures

NCI and the National Institute of Environmental Health Sciences (NIEHS) continue to support interdisciplinary **collaborations for improving research tools** used in etiologic studies of cancer and risk assessment. For example, these institutes are funding centers for the study of breast cancer risk associated with environmental exposures and several projects to support the use of geographic information systems in cancer epidemiology and control studies.

NCI scientists are using innovative **nanotechnologies in molecular profiling** to examine chromosomal alterations and changes in protein levels following exposure to environmental carcinogens. For example, scientists have found that changes in the levels of proteins following alteration of their gene precursors by the biochemical process of methylation are associated with the development of cancer.

Discovering and Characterizing Cancer Predisposing Genes in High-Risk Families

NCI's **Interdisciplinary Studies in the Genetic Epidemiology of Cancer** emphasize case-control and familial studies of gene-environment interactions for various forms of cancer. NCI-supported work includes a consortium of investigators searching for pancreatic cancer susceptibility genes, the Colon, Breast, and Ovarian Cancer Family Registries (CFRs), a high-risk families tissue resource, and other family registries and collaborative groups working to identify susceptibility genes for prostate cancer and other familial cancer syndromes including melanoma, renal cancer, testicular cancer, and brain tumors.

The **Cancer Genetics Network** (CGN) is a major NCI-supported infrastructure for studies of persons at high risk for developing cancer and for related translational research. CGN pilot studies combine existing and prospectively collected data to discover potentially important gene-environment interactions. The Network holds epidemiologic data on participants consistent with data collected by other NCI-supported consortia and registries, allowing the information to be used either independently or in combination with other groups. The CGN implemented and improved upon a state-of-the-art clinical trials informatics system (Trial-DB) across all Network sites.

Developing and Improving Resources for Gene Discovery and Characterization

NCI is providing readily available resources to support researchers studying gene-environment interactions in cancer causation, including the following:

- The **Cancer Genome Anatomy Project** (CGAP) continues to provide genomic resources for identifying and studying cancer genes. For example, CGAP's Mammalian Gene Collection establishes reference clones validated by sequence analysis for research use and has importance for both *in vitro* and population-based studies. The SNP500 program provides sequence verification of single nucleotide polymorphisms (SNPs). SNP500 will also develop assays for the Cohort Consortium, making all information immediately available on the Web. (For more information on these and other CGAP programs, see pages 16-17.)

CGF researchers develop and validate assays for gene sequence verification in conjunction with the SNP500 cancer program.

- NCI has developed a high-throughput **Core Genotyping Facility** (CGF) to support case-control and cohort studies in partnerships with the National Human Genome Research Institute, the Centers for Disease Control and Prevention, and academic and commercial organizations. The CGF provides high-throughput genotyping and gene sequencing, including verification of SNPs and other types of genetic variations. The Facility is also a test site for the development of policies, systems, and infrastructure to expedite data analysis of large-scale interdisciplinary studies and to enhance data sharing.
- CGN has substantially increased the number of participating patients and family members in its **biospecimen repository**.
- CFRs are developing a **repository of EBV-transformed cell lines**[1] from patients and selected family members for use by researchers.
- The **Gail Model** is a statistical tool to help estimate a woman's risk of breast cancer based on a number of predisposing factors, including family history. A study examining mammographic density as a risk factor for breast cancer development was completed recently, showing this characteristic reliable enough to be formally included in the model.
- NCI continues to support **workshops to develop collaborative studies** between population scientists and groups developing mouse models of cancer for the localization and characterization of cancer susceptibility genes.

Improving Quality Control Measures to Maximize the Value of Specimens

Biological specimens collected from patients, people at risk for cancer, and their families must be processed and stored according to strict requirements. This level of care is needed to ensure that the specimens are of sufficient quality to be used in a wide variety of assays and test procedures. NCI and partners are helping to develop and disseminate procedures to safeguard the quality of such samples. For example:

- CFRs support academic-commercial **biotechnology partnerships** to establish an integrated and standardized infrastructure for the collection and management of biospecimens from large populations, the production of related microarrays, and the development of novel relational data management software for associated molecular, clinical, and risk factor data.

[1] Cells taken from individuals normally do not live long *in vitro*. Cells "transformed" by *in vitro* infection with Epstein-Barr virus (EBV) will live and replicate indefinitely, providing a ready supply for research.

- CGF activities include sponsorship of **conferences on specimen handling and quality control** for DNA storage and analysis.
- NCI's intramural Epidemiology and Carcinogenesis Faculty has sponsored national **workshops on how to process specimens** to optimize their use in conjunction with current technologies. This faculty also helped found the International Society for Biological and Environmental Repositories, which developed a **"best practices" document** for the collection and storage of specimens.
- A series of NCI-supported studies have established an **optimal protocol for collecting oral epithelial cell samples** for genetic testing from large populations by mail, and pilot work has established acceptably high rates of compliance by study populations. Progress has been made in addressing issues of potential DNA damage by irradiation of samples during transport through the mail.
- The NCI Center for Bioinformatics has recommended a set of **informatics standards, guidelines, and procedures** for handling and storage of biospecimens.

Development

Supporting Intervention Trials and Translational Research on Inherited Susceptibility

NCI scientists and CGN are conducting a collaborative, prospective **study of risk reduction in women at high genetic risk for breast and ovarian cancers**. Researchers are comparing and evaluating two risk reduction strategies: preventive removal of the ovaries and fallopian tubes and a novel screening strategy. Investigators will include the impact of these procedures on quality of life in their evaluation.

NCI is also collaborating with the National Surgical Adjuvant Breast and Bowel Project to **genotype participants in the Breast Cancer Prevention Trial**, which showed that tamoxifen reduced the risk of breast cancer among high-risk women. Collaborators will focus on determining if variants in genes related to estrogen and tamoxifen metabolism can identify subsets of women who might be more or less likely to benefit from tamoxifen.

NCI is researching **alternative screening techniques for early breast cancer detection** in women genetically at risk for the disease. These include magnetic resonance imaging (MRI), positron emission tomography (PET) imaging, and *in vitro* analysis of cells obtained from breast duct lavage.

GENES AND THE ENVIRONMENT

GOAL

Discover those genetic, environmental, and lifestyle factors and their interactions that define cancer risk and that can inform the development and delivery of new strategies for prevention, early detection, and treatment.

Objectives and Fiscal Year 2005 Milestones and Required Funding Increases

Discovery

1. Identify susceptibility genes, haplotypes, and epigenetic events, and their interactions with environmental factors in cancer causation. $32.00 M

- Continue to investigate interactions among susceptibility genes, haplotypes, and environmental risk factors through support to the Cohort Consortium:
  - — Plan and support studies of additional cancer sites, using the results of the study of hormone-related variants and breast and prostate cancer. $5.00 M
  - — Increase the number of study participants and cancer types, enhance population diversity, and augment the biospecimen repository by continuing to expand the number of participating cohorts. $3.00 M
- Continue to investigate gene-environment interactions in lymphoma, brain, melanoma, prostate, and other selected cancers through case-control consortia. Fully support population-based and hospital-based studies to analyze pooled data for genetic and environmental susceptibility factors. $1.00M
- Conduct new initiatives in resequence analysis of genes chosen from known biological pathways or identified by microarray expression or comparative genomic hybridization analysis.
- Study cancers of high lethality by combining data from several studies using a consortial approach. $15.00 M
- Study populations at low risk of cancer to identify genes that may confer resistance to tumor development and environmental factors that may modulate the effect of these genes. $8.00 M
- Provide a forum for developing innovative new investigations through a consortium of groups capable and willing to conduct site-specific, case-control, and consortial studies.

2. Develop new ways to assess and measure environmental exposures for use in population studies. $6.00 M

- Continue to develop new noninvasive techniques for collecting and analyzing genes and gene products in very small biologic samples by expanding the Innovative Molecular Analysis Technologies Program. $2.00 M
- Continue to apply and validate measures of the cumulative cellular, genetic, and molecular effects of environmental exposure through funding supplements for ongoing research programs. $3.00 M
- Develop improved measures of nutrition and energy balance and of components of tobacco use. $1.00 M

3. Identify cancer predisposing genes in high-risk families and investigate how other genes and environmental factors modify expression of these genes. $11.00 M

- Extend studies and the geographical and population diversity of registries for familial cancers as well as additional heritable cancer sites in the United States, in cooperation with the Surveillance, Epidemiology, and End Results Program (population data) and Cancer Centers/Specialized Programs of Research Excellence (patient data). $4.00 M
- Expand the family registries for breast, ovarian, and colon cancers. $7.00 M

4. Develop and improve tools and infrastructures for the study of gene-environment interactions in human populations. **$11.00 M**

- Continue to maximize the quality, efficiency, and cost-effectiveness of specimen collection, processing, storage techniques, and high-throughput assays for human population studies and develop pilot feasibility projects for regional genotyping facilities. $3.00 M
- Develop with other NIH institutes a comprehensive informatics system to capture store, analyze, and integrate the expanding amount of information generated by studies of gene-environment interactions. $4.00 M
- Accelerate identification, validation, and development technologies for genetic epidemiology studies through the Cancer Genome Anatomy Project. $1.00 M
- Facilitate the localization of cancer susceptibility genes in humans and determine their function, by supporting the Mouse Models of Human Cancers Consortium, which has targeted mouse models in breast, colon, prostate, and pancreatic cancer. $3.00 M

Development

5. Support collaborative studies of high-risk individuals to address the clinical, behavioral, and societal issues associated with cancer susceptibility. **$12.00 M**

- Facilitate studies of outcomes for early detection, diagnosis, and treatment of genetically high-risk individuals, especially those from minority and underserved populations, through resources provided by the Cancer Genetics Network.
- Expand development of effective strategies to communicate cancer risk information to high-risk persons, patients, healthcare providers, and the public and maximize the recipients' abilities to make decisions and choices. $4.00 M
- Refine cancer risk prediction methods/models to integrate genetic and environmental determinants of cancer among diverse populations. $1.00 M
- Study the screening and treatment choices and preventive and other health behaviors of cancer survivors and persons at known genetic risk or in families with a high prevalence of cancer. $2.00 M
- Conduct observational studies, and trials where appropriate, of the long-term risks and benefits of currently used cancer risk reduction strategies (e.g., surgical, drug) for genetically high-risk individuals. $5.00 M

Management and Support **$ 1.15 M**

Total **$73.15 M**