ENVIRONMENTAL RISK FACTORS AND CANCER

Testimony Of

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Thank you, Senator Mack and Senator Feinstein, for inviting me to address you today. I am Susan Sieber, Deputy Director of the National Cancer Institute's (NCI) Division of Cancer Epidemiology and Genetics at the National Institutes of Health (NIH). With the twenty-fifth anniversary of the passage of the National Cancer Act, the NCI has entered into the most exciting time in its history. The pace of scientific discovery in fields such as cellular biology and molecular genetics, and in population-based multidisciplinary studies continues to accelerate, fueled by the development of innovative new technologies. These technologies and the experimental and epidemiologic approaches they support are focused on gaining a better understanding of the causes of cancer--including environmental exposures--and developing strategies for prevention.

Cancer Genetics

It is now widely recognized that cancer is a genetic disease since it involves one or more alterations in DNA or mutations in a gene. Many cancers occur in both a hereditary and a sporadic (nonhereditary) form. Cancer susceptibility genes are relatively rare, but the cancer risk for the individual carrying the gene can be very high. The recently discovered BRCA1 and 2 genes are examples of this type of mutation. Indeed, it is thought that mutations in these genes are responsible for a majority of hereditary breast cancer which is estimated to represent about 10% of all breast cancer. Far more frequently occurring are minor variations in genes, called polymorphisms, although the effects of gene polymorphisms by and large are not as dramatic as single gene mutations such as in BRCA1/2 or in Li-Fraumeni syndrome.

What does this have to do with environmental cancer? Quite a lot we think, because we are already finding that environmental agents interacting with genes can markedly affect a person=s likelihood of developing cancer. Before describing some of our efforts in this exciting and very promising area of gene-environment interactions, I would like to provide a brief overview of NCI's research program in environmental cancer.

Environmental Factors

NCI has had a long history of leading the effort to determine the extent to which environmental and occupational agents contribute to the burden of human cancer. We have a broad and wide-ranging research program of laboratory and epidemiologic investigations into the links between cancer and exposures to pesticides, air pollution, drinking water contaminants, electromagnetic and ionizing radiation, lifestyle choices, and other associated factors. We have also systematically mapped cancer mortality patterns in the U.S. over the last 40 years and aggressively pursued a highly successful program of field studies in high-risk areas in order to identify the reasons for geographic Ahot spots@ and other unusual cancer mortality patterns. Time does not permit presenting NCI=s portfolio of environmental research, so I have provided some documents which I think will give you some idea of our involvement in this area. Table 1 presents a partial listing of environmental agents (67 of them, from acrylonitrile to zinc) which have been or are being evaluated and includes not just environmental chemicals but also radiation, drugs, and biological agents.

Industrial workers have long served as sentinels for the general population with regard to environmental hazards, and much of the epidemiologic research undertaken to date has focused on these groups. Exposures in an occupational setting are usually longer in duration and at higher levels compared with environmental exposures. While I will not be discussing occupational exposures per se today, it should be understood that NCI places great emphasis on studies of cancer risks associated with occupational and industrial exposures, and a large number of such studies have been, or are being, conducted. While by no means exhaustive, the list of occupational groups being studied includes acrylonitrile workers, beauticians, dry cleaners, farmers, lawn care service workers, radiologists, and truck drivers. A more complete list of 47 occupational groups is provided as Table 2. In fact, one of NCI's newest branches, the Occupational Epidemiology Branch, is dedicated to this effort. A partial listing of some important studies of environmental and occupational cancer are listed in Table 3, and I would like to briefly highlight one or two of these studies.

In an ongoing study of drinking water quality in Iowa, NCI epidemiologists are estimating the cancer risks associated with consuming chlorination byproducts in drinking water. This study will evaluate the risk of cancers of the bladder, colon, rectum, pancreas, brain, and kidney associated with water quality data from residential history information plus an historical survey of Iowa public water supplies. Special attention will be given to effects of groundwater, which may be contaminated by seepage of pesticides, industrial solvents, and hazardous waste products.

In another study, a collaboration with NIEHS and EPA, we have launched the nation=s largest epidemiologic study of farmers and their families. The Agricultural Health Study will identify and assess factors that may account for previously reported cancer excesses among farmers. About 100,000 farmers, spouses and children of farmers, and pesticide applicators will be involved to assess both cancer and noncancer health (e.g., reproductive and neurologic) endpoints that may also be associated with farm practices

and lifestyles. In addition to studying occupational exposures of farmers themselves, the investigators will study the health of farm-family members who may also be exposed to lower levels of the same potential farming hazards. This portion of the study may be especially relevant to the general population since chemicals traditionally associated with agriculture (pesticides, fertilizers) can now be commonly found in urban areas. Monitoring will include environmental (air, water, food, soil, house dust) and biological (urine, blood) sampling, which will be coupled with information obtained from interviews and diaries. Researchers plan to monitor about 20 different pesticide-related activities and assess the average exposure and implications of each activity.

Gene-Environment Interactions

In other studies of environmental cancer, scientists are using modern genetic technology to look at interactions between common environmental agents and genes which might influence susceptibility. In one such study, scientists have sought a relationship between polymorphisms in the gene which determines the rate at which people detoxify certain chemicals through the action of an enzyme known as N-acetyl transferase. They divided women into two groups--those who were rapid detoxifiers and those who were slow--and looked at their risk for breast cancer as a function of how many cigarettes they smoked and for how long. They found that in women who are fast metabolizers, there were no real differences in breast cancer risk among the groups of nonsmokers, light, and heavy smoking women. For women who are slow metabolizers, however, there was an increasing risk for breast cancer with increasing numbers of cigarettes smoked. These intriguing results need to be confirmed, of course, but they do suggest an interaction between metabolic phenotype, environmental exposure, and cancer risk.

In another study, scientists are evaluating the possibility of gene-environment interactions in Seveso, Italy where an explosion in a factory in 1976 led to contamination of the area with dioxin. It is known that dioxin binds to a receptor outside of the nucleus of cells, is translocated into the nucleus, binds to a specific sequence of DNA, and thereby increases the activities of the enzymes involved in metabolizing dioxin. It is known that genetic polymorphisms for inducing the enzyme exist, and scientists are now looking at the implications of such a polymorphism in determining the risk for dioxin-induced disease.

The identification of gene-environment interactions through studies of genetic polymorphisms is very promising, and many studies are underway or in the planning stage. To look for interactions between the environment and germline mutations of major genes such as BRCA1/2 and p53 is much more difficult. The difficulty arises because these mutations are relatively rare in the general population, their penetrance is not known, and they require much larger numbers of subjects for study. To address these difficulties, NCI is planning to launch several exciting new initiatives. One such initiative is the Cancer Genetics Network, which will provide a research infrastructure in which study populations can be assembled at multiple participating centers with scientific and medical expertise in cancer genetics. These Network centers, which will be scattered around the country, will be multidisciplinary, collaborative centers of excellence in cancer genetics from which a variety of studies on familial cancer and cancer

susceptibility genes, including environmental exposures that interact with susceptibility genes, can be launched.

Another new initiative is the Cancer Genome Anatomy Project. This ambitious project involves identifying all the genes expressed in cancer cells. The goals of this program are to produce a full catalog of expressed genes for normal, premalignant, and cancer cells, as well as to provide for the development and application of new technologies to apply these indices for cancer detection and etiologic purposes. By recognizing the "molecular fingerprint" of each cancer cell--that is, by being able to read the information unique to each type of cancer and the message a triggering agent imparts to that cell--we will have an opportunity to learn how best to interrupt or reverse the carcinogenesis process.

Agency Collaborations

NCI's mandate is to conduct and support a broad-based program of research in cancer risk factors, diagnosis and detection, treatment, and prevention. Although as a research institution, we are not involved in the regulatory process, we interact freely and often with our sister regulatory agencies, providing them with relevant research results and data to assist them with their regulatory and policy-making decisions. NCI collaborates with a number of groups in these efforts and with occupational and environmental health specialists from academic institutions. One such collaboration is the Agricultural Health Study which was mentioned earlier, a joint project with NIEHS and EPA. Another is the Long Island Breast Cancer Study Project which the NCI was directed to launch in 1993. This project, which is being carried out with help from NIEHS, EPA, and academic institutions in the New York area, is looking into a variety of environmental factors which might be contributing to the elevated breast cancer rates reported on Long Island. A portion of the study is dedicated to assessing past and current exposures to a variety of environmental agents such as automobile and airplane exhausts, water pollutants, pesticides, toxic waste sites, and electromagnetic radiation. This aspect of the study is requiring considerable effort to develop new techniques and procedures for exposure and risk assessment, including development of biomarkers. It is anticipated that this investment will be amply repaid, as these methods will be readily applicable in future molecular epidemiologic studies of breast and other cancers at other sites around the country. Another aspect of the project, a case-control study of all breast cancers diagnosed in Nassau and Suffolk Counties on Long Island and Tolland and Schoharie Counties began in September of 1996. It is anticipated that this project will continue into 1999. In addition, Interagency Agreements with the EPA and the National Institute for Occupational Safety and Health (NIOSH) at the Centers for Disease Control and Prevention (CDC) provide formal mechanisms for exchange of information and for collaboration on other topics of mutual interest. For example, NCI and EPA share a long-standing interest in, and support for, studies of tumors occurring in fish and other marine animals which may represent sentinels for carcinogenic contaminants in the nation's waterways. Similarly, NCI and CDC have jointly followed a cohort of farm families accidentally exposed to high levels of PBBs during the 70s, looking at a variety of health endpoints, including risk for breast and other cancers. Other NCI collaborations in environmental cancer include NIOSH (an acrylonitrile study), Department of Agriculture

(a migrant agricultural worker study), and the Department of Energy (a study on EMF and brain cancer). This collaborative approach allows for an effective coordination of the Federal research effort and an efficient use of research appropriations.

Future Directions

Where do we go from here? The era of genetic medicine is upon us. Indeed, the field of cancer genetics yields an extraordinary opportunity for new investments in research. To capitalize on the opportunities and challenges in cancer genetics, we must understand the messages that normal cells, cancer cells, and the agents triggering mutations are telling us. NCI has established a successful program of Cooperative Family Registries for Breast Cancer, and registries for cancers at other sites will follow. These registries support the coordinated collection of data and biological specimens, and evaluate patterns of inheritance in cancer-prone families. It is our expectation that these registries will provide the tools and resources needed to further clarify gene-environment interactions in determining cancer risks. The Cancer Genetics Network I mentioned earlier may also serve as a platform from which to launch studies on environmental cancer. These and similar programs will be our best means for identifying the causes of cancer and strategies for prevention.

In the meantime, it is clear that a better understanding of environmental cancer is possible through advances in genetic technology. Our efforts are directed toward determining which individuals are susceptible to genetic changes from environmental carcinogens, which agents are directly responsible for genetic changes that lead to cancer, and how such changes can be avoided or reversed.

Until more definitive data is available, we have a responsibility to help the public understand how environmental exposures affect cancer risk. We must also do more to clarify whether the risks are strong or relatively weak, keeping in mind that almost nothing can be guaranteed to be completely "safe" Thus, one must weigh the benefits of an environmental agent against its risks in an ongoing process which takes into account the most recent scientific findings.

This concludes my statement. I would be pleased to answer any questions you may have.