Cancer remains the second leading cause of mortality in the United States today, resulting in more than half a million deaths each year. Recent data have shown a downward trend in mortality rates due to cancer—in large part due to better survival as a result of early detection and improved therapies. Despite this trend, the incidence of some cancers is on the rise.

Since the enactment of the Cancer Act of 1972, a wealth of knowledge has been collected about cancer because of significant investments made in fundamental and applied research. One of the most surprising discoveries is that cancer is not a single disease. It is, rather, a closely linked group of molecular disorders, varying in etiology and mechanisms, with some common intersections. Another complexity of the disease is that not everyone exposed to a particular cancer-causing chemical will develop cancer. This is due to the complex interactions that occur between environmental and genetic factors—both of which are known to be involved in the development of cancer.

On May 16–17, 2001, the Roundtable on Environmental Health Sciences, Research, and Medicine convened a workshop to begin understanding the complex interactions between genetics and environmental factors and their relationship to cancer. This workshop came at an ideal time to examine the interaction, according to Samuel Wilson, National Institute of Environmental Health Sciences, because of two recent advances in genetics and environmental studies. The first advance is the completion of an initial draft sequence of the human genome. As researchers are now in the early stages of the postsequencing genomics era, they are beginning to comprehend the genetic variations that modify an individual’s susceptibility to cancer. The second development is the...
evolving, expanded, and enhanced view of environmental health and exposures that includes factors such as diet, life-style, metabolic alterations, socioeconomic status, and environmental pollutants. It is this expanded view of environmental health that will allow more meaningful and precise studies of environmental contributions to cancer.

**Research Reveals the Complexity of the Relationships Between Genes and the Environment in the Development of Cancer**

Understanding the contribution of environmental factors in the development of cancer has been and continues to be an active area of research. One of the earliest insights into the environment’s contribution to the development of cancer was in 1775, when the British surgeon, Percival Pott, discovered a cluster of scrotal cancer among young chimney sweeps exposed to soot (see Figure 1). Subsequent research found that the soot contained mixtures of carcinogenic polycyclic hydrocarbons. In a scientific keynote address at the workshop, Joseph Fraumeni, National Cancer Institute, pointed to a growing body of knowledge that dramatically illustrates the influence of environmental factors in the initiation and progression of cancer.

John Milner, Pennsylvania State University, described discoveries that both essential and nonessential dietary nutrients can markedly influence several key biological events—including cell cycle regulation, processes involved with replication or transcription, immunocompetence, and factors involved with apoptosis, or programmed cell death. These findings have strengthened convictions that specific foods or components may markedly influence cancer risk.

**Cancer as a Genetic Disease**

Analyses of the incidence of cancer in twin pairs and in families are traditional methods for answering questions about the relationships between cancer etiology, genes, and the environment. Kari Hemminki, Karolinska Institute, and Curtis Harris, National Cancer Institute, described recent progress in identifying and characterizing highly penetrant susceptibility genes in familial cancer—work that has revolutionized our understanding of the critical genetic mechanisms in cancer etiology. Studies that combine genetic analysis with assessment of exposures and diet can explain why not everyone exposed to a particular cancer-causing chemical will develop cancer. Recent research has identified functional polymorphisms that influence an individual’s cancer risk and has focused on gene products involved in activation and de-
toxification of carcinogens and DNA repair. Gene polymorphisms that are important in apoptosis will increasingly be recognized as clues to individual susceptibility to cancer.

Disparities in Cancer Rates Emphasize the Importance of Environment

Despite recent good news about decreasing cancer mortality rates, not all population subgroups share in this success. Cancer rates are higher and accelerating among some racial and ethnic groups. The reasons for these disparities clearly include the environment, hormones, and genetics. Lovell Jones, M.D. Anderson Cancer Center, described how progress toward preventing, diagnosing, and treating cancer will be hampered by the nation’s inability to deal effectively with the greater cancer burden borne by certain vulnerable populations. These vulnerable populations are typically defined as groups at higher-than-average risk of death, disease, and disability, and include people with low incomes, low literacy rates, the elderly, rural communities, African Americans, Hispanics, American Indians and Alaska Natives, and other ethnic minorities.

New approaches may be needed to assess how genes and the environment compound cancer risk in populations considered vulnerable because of their social or economic status, said some workshop participants. Demographic studies of cancer must consider the diversity within affluent groups as well as within less economically affluent groups, said Armin Weinberg, Baylor College of Medicine. They also must consider immigration patterns and countries of origin because those factors play a primary role in predisposition to cancer.

![Figure 2. Comparison of prostate and breast cancer in different countries. SOURCE: Griffiths et al. (2001). Reprinted with permission by Comp Graphics Services, UK.](image)
Special populations, such as migrant farm workers and children, are particularly vulnerable to developing cancer following environmental exposures for a variety of reasons. Farm workers endure an exceptionally high burden of exposure to pesticides and other agents that are known carcinogens, according to Maria Hernandez Valero. Socioeconomic conditions require that pregnant women and children are often in the fields. Teratogenic risks have been documented in unsuccessful pregnancies and births of children with birth defects following in utero exposure to agricultural chemicals. It is particularly difficult to study exposures and cancer clusters in migrant farm workers because they are mobile and hesitant to be subjects of investigation, said Richard Jackson, Centers for Disease Control and Prevention.

Environmental Factors Can Play an Early Role in Childhood Cancers

Children are vulnerable to environmental exposures starting in infancy. Further, the developing child may be particularly sensitive to exposures affecting specific organs, since the types of cancer found in children are significantly different from those found in adults. Greta Bunin, Children’s Hospital of Philadelphia, and Leslie Robison, University of Minnesota, discussed trends in incidence and survivorship in childhood cancers and presented preliminary evidence about linkages between childhood cancer and diet. In addition to in utero exposures, and in some cases preconceptual exposures of the parents, diet, and other environmental influences may combine with genetic predispositions to form a strong link between these factors and the development of childhood cancers. Some meeting participants agreed that longitudinal studies are needed to more carefully identify risk factors.

Environmental and Genetic Factors Combine to Affect Site-Specific Cancer Rates

Presenters described some recent advances in understanding the linkages between genes and the environment in site-specific cancers, including breast, lung, colorectal, and prostate cancer. More refined studies have focused on learning how individuals respond differently to harmful substances. For example, John Minna, University of Texas Southwestern Medical Center, and Margaret Spitz, M.D. Anderson Cancer Center, described how some genes signal the making of enzymes in the lungs. Ordinarily these enzymes, or active substances, destroy some of the cancer-causing substances in tobacco smoke, but a gene variation might reduce these enzymes and increase susceptibility to lung cancer. Evidence of familial aggregation of lung cancer provides indirect support for the role of genetic predisposition to lung cancer. These patterns of inheritance studies suggest that a small proportion of lung cancer is due to “lung cancer genes” that are probably of low frequency, but of high penetrance. However, exposure to a carcinogen is also key.

There is probably an important environmental role in the development of colorectal cancer based on the variance in the incidence of the disease. Presentations by Raymond DuBois, Vanderbilt University, and David Alberts, Arizona Cancer Center, highlighted what is known about environmental risk factors. There is a 20-fold variation in incidence rates in different geographic regions around the country, in-
indicating that genetics and environmental and life-style factors play a role in etiology. For example, because adenomatous polyps are precursors to colorectal cancer, assessing the effect of environmental and genetic factors in adenoma occurrence and recurrence might help identify relatively asymptomatic individuals who are at increased risk of cancer and who would benefit most from an overall public health intervention.

Development of multigenic models of cancer susceptibility will be an important future approach to predicting, preventing, and diagnosing some cancers, said participants. Prostate cancer, for example, is a common disease for which there are few well-established risk factors. Pedigree analyses suggest a genetic component for some individuals; however, a single-gene model cannot explain the majority of prostate cancer cases, thus, suggesting a multigenic etiology. Moreover, the international and racial–ethnic variations in prostate cancer incidence (see Figure 2), combined with the effects of migration on risk patterns, suggest that genetic factors are likely to play a central role in determining prostate cancer risk. Traditionally, native Japanese and Chinese men have the lowest incidence of prostate cancer. However, when Asians migrate to the United States, which has a higher incidence rate, their risk increases. Participants speculated that the differences between various incidence rates may be due to testosterone biosynthesis or metabolism, as well as environmental influences.

Moving Forward: What the Future Holds

This year alone, approximately 560,000 Americans will die of cancer-related causes and almost 1.4 million new cancer cases are expected to be diagnosed. Despite these numbers, the data presented at the workshop reinforced that progress is being made in the war against cancer. Most speakers noted that it was an exciting time to be in cancer research because treatment or cures are becoming increasingly effective. This workshop laid out a number of observations and strategies for the future of cancer research.

Disparities. The success that has been seen thus far in the war against cancer is not equally accessible to all individuals or groups. The populations with disparities include Hispanics, American Indians, Alaska Natives, Asian and Pacific Islanders, African Americans, Native Hawaiians, blue-collar workers, rural, elderly, low-income, and low-literacy groups. They not only carry a higher burden of cancer, but are also more prone to other diseases and societal problems. Moreover, the burden of cancer is disproportionately borne by the poor and the undereducated, as well as by populations at higher risk due to life-style, environmental exposure, or genetic susceptibility. Achieving better cancer care and control within these underserved and high-risk populations is an extremely important goal. As several speakers emphasized, while trying to achieve this goal, we must remember, “one size does not fit all.”

Cancer Prevention. Presentations throughout the two days highlighted the fact that investigating cancer in populations has identified many life-style and environ-
mental carcinogens and this knowledge has led to new approaches for reducing cancer risk. Yet, there is still much to learn about the causes of cancer, particularly why one person with the same cancer-causing exposure (such as smoking or diet) develops cancer, whereas another does not. Individuals’ genetic makeup can affect their risk of developing cancer in ways more subtle than those seen in familial cancer syndromes. Variations in genetic susceptibilities related to how individuals control and respond to endogenous hormone levels, diet, exposure to carcinogens, sun, and infectious agents are likely to influence a given individual’s chance of developing cancer.

Future Research Areas. Development of multigenic models of cancer susceptibility will be an important future approach to predicting, preventing, and diagnosing some cancers, said participants. Even when there is evidence of genetic predisposition, however, future research efforts must focus on gene–environment interactions to fully develop effective cancer prevention and treatment strategies.

Cancer Registries and Large Populational Studies. During the workshop, a number of cancer registries were discussed, including the National Cancer Institute’s (NCI’s) Surveillance, Epidemiology, and End Results program and the Kentucky Cancer Registry, and also about large population studies (more than 100,000 individuals) sponsored by the NCI and the American Cancer Society. Several participants suggested that the cancer registry data be combined with other databases to identify new etiologic leads. For example, cancer registry data could be combined with population survey data or environmental data, such as pesticide usage or hospitalizations. Participants also noted the need for a linked environmental surveillance system. If cancer clusters were identified within the context of a nationwide childhood cancer registry, one could identify similar areas in the United States and look for similar types of clustering. Finally, there are approximately 80,000 industrial chemicals now registered for use, but very few have been tested for their health effects singly, synergistically, or with different kinds of genetic patterns. Hazard assessment for environmental chemicals is essential and would likely require the collaboration of many federal agencies and the private sector.

Research Implications. This workshop highlighted a number of potential research implications. Individuals discussed the needs for additional collaboration in multidisciplinary research. One speaker discussed the need for more discovery-driven research to define the molecular landscape of cancer. This research needs to be combined with epidemiological and animal research to fully understand the potential therapeutic implications. Further, some researchers suggested continuing the trend of investing in research on the preclinical stages of cancer and on early diagnosis.

Some speakers stressed that this research must include the community. If cancer is in the community, then the solution needs to be in the community. In order to do this, we as researchers must enhance our skills and develop better techniques in the area of risk communication. Individuals in the community are looking for answers, but often are frustrated.
Handling issues related to technology transfer will continue to be important in order to advance research results.

Additionally, broad access to population group data must be allowed, but patient consent and patients’ rights must be guarded. There will be a number of ethical, legal, and social implications of genetic research that have to be defined and debated. Handling issues related to technology transfer will continue to be important in order to advance research results. The science community will have to provide guidance in these areas to Congress and the public.

Overall, many participants felt that we were making tremendous strides in the war on cancer. People felt that being diagnosed with cancer is no longer a death sentence, and that the future holds promise for further progress in both treatment and prevention.
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