In July 2012, Joseph F. Fraumeni, Jr., M.D., reached a career milestone of 50 years at NCI. He marked this anniversary by stepping down as Director of DCEG, while continuing to serve as a senior investigator and advisor at NCI and NIH.

“Throughout his 50 years at NIH, Dr. Fraumeni has distinguished himself by his creative and diligent pursuit of the causes of cancer, both genetic and environmental. He has been universally recognized for his intellectual contributions to—and inspired leadership of—the field of cancer epidemiology,” said NCI Director Harold Varmus, M.D. “Furthermore, he has almost single-handedly built the remarkable, even enviable, epidemiology division at NCI, an intramural program in which scientists continue to study the origins of cancer with tools that range from the population to the molecular level.”

Dr. Fraumeni received an undergraduate degree from Harvard College, an M.D. from Duke University, and an M.Sc. in epidemiology from the Harvard School of Public Health. After completing a medical residency at Johns Hopkins Hospital and the Memorial Sloan-Kettering Cancer Center, he joined NIH in 1962 as a commissioned officer in the U.S. Public Health Service (PHS). After a progression of leadership positions at NCI, Dr. Fraumeni became founding Director of DCEG in 1995, at which time he was promoted in the PHS to the rank of Rear Admiral and Assistant Surgeon General.

Throughout his years of leadership at NIH, Dr. Fraumeni shaped and directed a comprehensive epidemiological and interdisciplinary research program designed to identify the environmental and genetic determinants of cancer and the means of prevention. A continuing focus of his personal research has been the study of
genetic susceptibility to cancer, particularly by investigating familial aggregations of various cancers. Most notable was his discovery in 1969 with fellow NCI researcher Dr. Frederick P. Li of a rare, inherited syndrome manifested by a striking constellation of multiple cancers in children and young adults. This observation eventually led to collaborative molecular studies that uncovered inherited mutations in the p53 tumor suppressor gene.

Another central theme of Dr. Fraumeni’s research has been the search for lifestyle and other environmental causes of cancer. In 1975, he led the development of the first in a series of computer-generated maps depicting geographical variation of U.S. cancer mortality at the county level. This work allowed Dr. Fraumeni and his colleagues to develop a way to identify the environmental exposures driving the distinctive patterns of certain malignancies and also to target high-risk areas for measures aimed at cancer prevention and control.

Dr. Fraumeni’s recent work has centered on the integration of genomic and other emerging technologies in efforts to dissect the genetic and environmental components of cancer and their interactive effects in the origins and progression of cancer. Toward this end, Dr. Fraumeni has been a leader in developing molecular epidemiology platforms and large-scale collaborative strategies to accelerate a fuller understanding of carcinogenic risks and mechanisms that will inform new clinical and public health interventions.

In recognition of his scientific achievements, Dr. Fraumeni has received numerous honors, including the Charles S. Mott Prize from the General Motors Cancer Research Foundation, the Abraham Lilienfeld Award from the American College of Epidemiology, the John Snow Award from the American Public Health Association, the James D. Bruce Award from the American College of Physicians, the Nathan Davis Award from the American Medical Association, the Alton Ochsner Award from the American College of Chest Physicians, the Medal of Honor from the American Cancer Society, and the Lifetime Achievement Award from the American Association for Cancer Research.

In addition, Dr. Fraumeni has been elected to membership in the National Academy of Sciences, the Institute of Medicine, the Association of American Physicians, and the American Academy of Arts and Sciences.

Dr. Fraumeni’s research contributions are documented in more than 860 scientific publications and books, including several editions of the definitive textbook Cancer Epidemiology.
“Dr. Fraumeni has been one of the leading contributors in cancer epidemiology, both because of his own innovative research and through the productive environment he has created at NCI.”

—Christopher Wild

assessing the contributions of someone’s scientific work is a complex process that strives to quantify the scientific, clinical, or public health significance of his or her publications. Such an evaluation reflects the investigator’s demonstration of leadership in the field; the mentoring and training of junior scientists; and the development of resources, technologies, and methodologies that galvanize research by other scientists. Several indices have been developed as benchmarks to estimate the overall impact of a scientist’s work. The two most commonly used are the Thomson Reuters Web of Knowledge Science Citation Index (SCI) and the h-index. The SCI indicates the number of articles that have cited a given publication, whereas the h-index estimates a scientist’s cumulative contribution by expressing the number of articles (h) that have received at least h citations. By any of these measures, the contributions of Joseph F. Fraumeni, Jr., M.D., are remarkable.

Based on an analysis conducted in August 2012, Dr. Fraumeni had more than 860 publications with more than 60,000 citations in the Web of Knowledge database; he also had an almost unheard of h-index of 121. Dr. Fraumeni’s top-cited publications include articles on Li-Fraumeni syndrome and the Wilms tumor-aniridia syndrome; the racial and geographic variation of cancer in the United States and internationally; the rising incidence of several cancers, including adenocarcinoma of the esophagus, gastric cardia, and kidney; studies of cancer risk among various immunosuppressed populations, including organ transplant recipients; the role of smokeless tobacco and alcohol in oral and pharyngeal cancer; the relationship between herbicide exposures and non-Hodgkin lymphoma; the impact of nutritional and antibiotic interventions on esophageal and gastric cancer in high-risk populations in China; the role of indoor air pollution in the high rates of lung cancer in China; and genome-wide association studies of breast, prostate, and several other cancers. Figure 1, showing the annual number of citations of publications that Dr. Fraumeni has written, demonstrates that his scientific impact shows no signs of waning.

—Shelia Hoar Zahm, Sc.D.

Measuring the Impact of Publications by Joseph Fraumeni

 Assessing the contributions of someone’s scientific work is a complex process that strives to quantify the scientific, clinical, or public health significance of his or her publications. Such an evaluation reflects the investigator’s demonstration of leadership in the field; the mentoring and training of junior scientists; and the development of resources, technologies, and methodologies that galvanize research by other scientists. Several indices have been developed as benchmarks to estimate the overall impact of a scientist’s work. The two most commonly used are the Thomson Reuters Web of Knowledge Science Citation Index (SCI) and the h-index. The SCI indicates the number of articles that have cited a given publication, whereas the h-index estimates a scientist’s cumulative contribution by expressing the number of articles (h) that have received at least h citations. By any of these measures, the contributions of Joseph F. Fraumeni, Jr., M.D., are remarkable.

Based on an analysis conducted in August 2012, Dr. Fraumeni had more than 860 publications with more than 60,000 citations in the Web of Knowledge database; he also had an almost unheard of h-index of 121. Dr. Fraumeni’s top-cited publications include articles on Li-Fraumeni syndrome and the Wilms tumor-aniridia syndrome; the racial and geographic variation of cancer in the United States and internationally; the rising incidence of several cancers, including adenocarcinoma of the esophagus, gastric cardia, and kidney; studies of cancer risk among various immunosuppressed populations, including organ transplant recipients; the role of smokeless tobacco and alcohol in oral and pharyngeal cancer; the relationship between herbicide exposures and non-Hodgkin lymphoma; the impact of nutritional and antibiotic interventions on esophageal and gastric cancer in high-risk populations in China; the role of indoor air pollution in the high rates of lung cancer in China; and genome-wide association studies of breast, prostate, and several other cancers. Figure 1, showing the annual number of citations of publications that Dr. Fraumeni has written, demonstrates that his scientific impact shows no signs of waning.

—Shelia Hoar Zahm, Sc.D.

Figure 1. The number of citations of publications written by Joseph Fraumeni, by calendar year.
In the 1960s, Joseph F. Fraumeni, Jr., M.D., and Dr. Robert W. Miller, in what was then the Epidemiology Branch of NCI, began an exploration into the epidemiologic patterns of childhood and familial cancer about which little was known. Their search began with a systematic multicenter study of childhood cancer that suggested an excess of certain congenital anomalies (e.g., aniridia with Wilms tumor) and multiple primary cancers in the same individual (e.g., adrenocortical and brain tumors). At the same time, Dr. Fraumeni began to investigate a series of cancer-prone families that he identified while making rounds at the NIH Clinical Center. These families became the foundation for the DCEG familial cancer registry, which continues to this day. As expected, most of the familial aggregations were confined to a single type of cancer, but a few families were found to have an unusual diversity of tumors that was difficult to explain.

Soon thereafter, a remarkable familial occurrence came to the attention of Dr. Frederick P. Li, a research colleague at NCI. In an almost explosive manner, several members of one family developed a variety of tumors, notably childhood rhabdomyosarcoma and breast cancer, but also other forms of cancer among children and young adults in the line of descent. This observation prompted Drs. Li and Fraumeni to return to the multicenter survey of childhood tumors and expedite completion of a study of children diagnosed with rhabdomyosarcoma and breast cancer. In 1969, they reported their findings in two landmark papers that appeared in the *Annals of Internal Medicine* and the *Journal of the National Cancer Institute.* The striking diversity of tumors was at variance with the prevailing notion that familial susceptibility to cancer is usually site- or tissue-specific (see Figure 1).

The spectrum of early-onset cancers was clarified in 1982, when Drs. Li and Fraumeni published in *JAMA* a 12-year prospective study of members of the original four families. There were 16 new cases of cancer, far exceeding expectations based on general population rates. The array of new cancers closely resembled the familial pattern that was initially reported. By the late 1980s, Drs. Li and Fraumeni had assembled 24 families with similar, well-documented manifestations of a multiple-cancer syndrome. A prospective study of all families provided epidemiologic evidence of an excess risk of diverse cancers affecting young people in a dominantly inherited pattern. Breast cancer and soft tissue and osteogenic sarcomas were especially prevalent, but the risks of acute leukemia, brain tumors, and adrenocortical neoplasms were elevated as well. As interest increased in this familial disorder, it generally became known as Li-Fraumeni syndrome (LFS).

As time passed, Drs. Li and Fraumeni collected biospecimens and collaborated with laboratory investigators using a variety of biomarkers to search for an underlying mechanism that might explain the familial susceptibility to multiple tumors. Success was limited, however, until collaboration with Dr. Stephen Friend and Dr. David Malkin at Harvard, along with Dr. Louise Strong at the MD Anderson Cancer Center, uncovered germ line mutations of the *p53* tumor suppressor gene in five consecutive families. The finding was quickly confirmed and intensified clinical and molecular interest in LFS, particularly because somatic mutations of *p53* also were reported in a large proportion of cancers arising in the general population.

The discovery of inherited *p53* mutations provided an opportunity for predictive genetic testing and clinical intervention aimed at the early detection and management of tumors in LFS. The finding also brought into sharp focus a series of clinical, psychological, legal, and ethical problems that would likely extend to other cancer susceptibility genes that seemed on the verge of isolation at that time. The issues prompted a series of NCI-sponsored workshops that published recommendations about predictive genetic testing in cancer-prone families.

Over the next two decades, LFS work continued mainly outside of NCI until 2010, when Sharon Savage, M.D., and Phuong Mai, M.D., both of the Clinical Genetics Branch, organized a workshop that brought together researchers, clinicians, and members of affected families. An international consortium was formed to develop effective cancer prevention and risk-reduction strategies for LFS families, provide a platform for developing a support group for LFS families, and create a registry and database of affected families.
families, and pool resources for further research into the biology and genetics of the syndrome. Working with other clinical investigators in the consortium, Drs. Savage and Mai launched a feasibility study to recruit LFS families into a new screening protocol study at NIH designed to identify effective methods for early cancer detection without the use of radiation, which is known to magnify the risk of cancer in p53 gene carriers. Efforts also are being made to understand and manage the psychosocial aspects of this disease among LFS patients as well as their relatives and caretakers. So far, the study has enrolled 118 families at NIH, with many additional families being seen at extramural locations. “Clearly, there is a desire across the LFS community for this type of study,” Dr. Savage said. “Families really want to do something to help understand and ultimately prevent this devastating disease.”

At the end of the workshop, Dr. Strong commented, “In the 1960s, studies of familial cancer generally focused on a single site, such as hereditary breast cancer. The initial description of a familial syndrome involving so many tumor types raised questions about the possibility of referral bias, chance events, or an environmental factor such as an oncogenic virus. It was the perseverance of Drs. Li and Fraumeni over 20 years; the prospective findings; and the convergence of clinical, epidemiological, and biological observations that convinced the medical and scientific community that there was, indeed, a distinctive syndrome of cancer susceptibility. The work of Drs. Li and Fraumeni reflects the power of the multidisciplinary approach of genetic epidemiology and its potential contribution toward a better understanding of cancer etiology and prevention.”

—Adapted from Fraumeni, 1995

Participants in the 2010 Li-Fraumeni syndrome workshop included researchers, clinicians, patient families, and advocates.

Figure 1. Pedigree of Family A from the first paper documenting the constellation of tumors in what would later be known as Li-Fraumeni syndrome. This family developed a remarkable combination of multiple cancers in children and young adults, including soft tissue sarcomas and breast cancer. The proband, noted by an arrow, was the first affected individual identified in the study. (Li F, Fraumeni JF, Jr. Ann Intern Med 1969)
O
n a door in the office of Joseph F.
Fraumeni, Jr., M.D., is a poster
containing a Chinese proverb attributed
to Confucius. This proverb roughly
translates as “When you drink the
water, remember who dug the well.”

For a majority of scientific
themes across the Division,
Dr. Fraumeni conducted seminal
work showing the promise of that
particular line of research.

Dr. Fraumeni is one of those rare
individuals who always remembers
and honors the mentors and scientific
leaders who paved the way. And yet,
for the more than 300 people currently
in DCEG, Dr. Fraumeni is the one
“who dug the well” that initiated their
research. For a majority of scientific
themes under study across the Division,
Dr. Fraumeni conducted seminal work
showing the promise of that particular
line of research for yielding clues to
cancer etiology and prevention. Under
his guidance, these research themes
have flourished and expanded.

The well-known work on what is
now called Li-Fraumeni syndrome
laid the foundation for the many studies
of familial cancer that Dr. Fraumeni
and others have conducted in DCEG.
These projects have had a significant
impact not only on scientific discovery
but also on the clinical management
of hereditary cancer syndromes and
related conditions. For example, by
studying families at high risk for
melanoma, DCEG researchers and
their collaborators established that dys-
plastic nevi are precursors to familial
and sporadic melanoma, identified the
first major susceptibility genes for mela-
noma, published a clinical pathology
atlas for melanoma and nevi, created
training videos on how to manage
high-risk families and individuals, and
developed the first calculator to estimate
an individual’s risk of developing mela-
noma. Special emphasis is now being
placed on determining the biological
mechanisms of melanoma susceptibility
through genome-wide association stud-
ies, exome sequencing, high-resolution
array-based comparative genomic
hybridization (array-CGH), chromatin
immunoprecipitation (ChIP) sequenc-
ing (used to analyze protein interactions
with DNA), and molecular profiling.

The search for high-risk susceptibil-
ity genes is under way for several other
familial cancers and precancerous syn-
dromes, both common and rare, such
as lymphoproliferative disorders; bone
marrow failure syndromes; chordoma;
osteosarcoma; and cancers of the ovary,
lung, testis, and bladder.

In 1967, in the first published report of
familial bladder cancer, Dr. Fraumeni
described what might be viewed as a
forerunner to DCEG’s interdiscipli-
nary investigations of familial cancer. In
striving to explain why bladder cancer
developed in a man and his three sons,
all of whom were smokers, Dr. Fraumeni
brought the affected and unaffected
family members to the NIH Clinical
Center for a study of tryptophan metab-
olism, which was suspected at the time
to play a role in bladder carcinogenesis.
Although the findings proved to be unremarkable, echoes of this approach reverberate in DCEG’s portfolio of studies that use molecular biomarkers to identify mechanisms of cancer susceptibility, including gene-environment interactions in familial and non-familial forms of cancer.

Although studies of genetic susceptibility to cancer remain a major focus in DCEG, Dr. Fraumeni and his colleagues began, in the 1960s, a series of investigations designed to identify the role of environmental and occupational exposures in cancer etiology. Most informative was the landmark report in 1969 of a study of copper smelter workers in Montana that revealed a significant dose-related excess risk of lung cancer associated with exposure to inorganic arsenic. This was the first indication that inhaled arsenic is a respiratory carcinogen, and the finding was sufficiently robust to prompt the Occupational Safety and Health Administration to set new federal occupational exposure limits.

A 1969 report on the study of copper smelter workers in Montana was the first indication that inhaled arsenic is a respiratory carcinogen, and the finding was sufficiently robust to prompt the Occupational Safety and Health Administration to set new federal occupational exposure limits.

In 1975, interest in environmental cancer was further sparked by the publication of the first NCI cancer mortality atlas, which mapped the death rates for cancer across the United States at the county level. In view of the earlier report that occupational arsenical exposure is carcinogenic, it was not surprising to find elevated rates of lung cancer in counties with arsenic-emitting smelters, but further studies with fellow NCI researcher Dr. William Blot revealed that the elevated risk extended beyond the workforce to the residential population exposed to arsenical pollution emitted by the plants.

The most dramatic geographic pattern for lung cancer was seen in the string of U.S. counties with markedly elevated rates along the southeast Atlantic coast. In a series of case-control studies conducted in this area with Dr. Blot and Robert N. Hoover, M.D., Sc.D., Director...
of the Epidemiology and Biostatistics Program, the researchers found that the excess lung cancer was due to asbestos exposures associated with short-term shipyard work that took place during World War II.

In recent decades, the expanding portfolio of occupational and environmental studies in DCEG has been strengthened by increasingly sophisticated methods of exposure assessment to identify specific carcinogens and quantify the risks involved. The studies continue to have an impact on regulatory and public health policies, as illustrated by recent studies of workers exposed to diesel exhaust, formaldehyde, benzene, trichloroethylene, and agricultural pesticides.

The initial publication of the U.S. cancer maps was soon followed by similar atlases from other countries. Most remarkable was geographic clustering of various cancers in China, motivating Drs. Fraumeni and Blot, along with their colleagues, to collaborate with Chinese scientists in a series of epidemiologic studies in high-risk populations of various cancers. In efforts to explain the elevated rates of lung cancer among nonsmoking women in northern China, case-control studies implicated indoor air pollution from coal-burning stoves and cooking oil volatiles in poorly ventilated homes.

More recent studies have focused on Xuan Wei province, which has the highest incidence of lung cancer in China, providing evidence for the International Agency for Research on Cancer to classify coal-combustion products as an established carcinogen. The research has extended to other high-risk populations in China and Asia, where genetic susceptibility markers for lung cancer have been identified through collaborative genome-wide association studies. Other ongoing studies instigated by geographic patterns include investigations of bladder cancer in northern New England; gallbladder cancer in Chile; and esophageal cancer in high-risk areas spanning the globe, including China, Iran, Kenya, and Brazil.

Dr. Fraumeni’s interdisciplinary approach to studies of high-risk populations continues to inspire lines of research across DCEG and around the world.

When Dr. Fraumeni arrived at NCI in 1962, he was asked to evaluate the potential cancer risk associated with exposure to polio vaccine that had been inadvertently contaminated with simian virus 40 (SV40), known to be carcinogenic in laboratory animals. Public health concern was intense, but Dr. Fraumeni’s report in JAMA in 1963 revealed no evidence of excess cancer risk among children who were exposed to those early batches of vaccine that contained SV40. When concern over SV40 resurfaced in the 1990s due to its apparent detection in human mesothelioma, brain, and other tumors, DCEG studies found that cancer risks did not increase among newborns and others who had received the SV40-contaminated vaccine.

In addition to studies of the role of infectious agents in cancer risk, most notably HIV/AIDS and human papillomavirus, recent attention has centered on the impact of immunological alterations and inflammatory processes in cancer susceptibility.
A series of epidemiological studies was launched to evaluate the cancer risk following immunosuppression related to underlying medical conditions and their treatments, including the first study, with Dr. Hoover, that quantified the excess risk of lymphoma and other cancers among solid organ transplant recipients. This report, published in The Lancet in 1973, became a forerunner of current record-linkage studies of transplant-related cancers that encompass the majority of the U.S. population.

Another long-standing interest of Dr. Fraumeni and his colleagues has been the risk of cancer following chemotherapy, hormonal therapy, and radiotherapy, including their interactions with genetic, immunological, and lifestyle factors. These studies became the cornerstone of the expanding portfolio of DCEG research in radiation and hormonal epidemiology. The studies described here represent only a few of Dr. Fraumeni’s early wide-ranging research projects that, in retrospect, anticipated the next half century of cancer epidemiology in DCEG and elsewhere. His interdisciplinary approach to studies of high-risk populations continues to inspire lines of research across DCEG and around the world.

—Shelia Hoar Zahm, Sc.D.

MARGARET TUCKER APPOINTED AS DCEG ACTING DIRECTOR

Margaret A. Tucker, M.D., Director of the Human Genetics Program, was tapped by Harold Varmus, M.D., NCI Director, to serve as Acting Director for DCEG while a search for a permanent director is conducted. Stephen J. Chanock, M.D., Chief of the Laboratory of Translational Genetics and Director of the Core Genotyping Research Laboratory (formerly the Core Genotyping Facility), and Robert N. Hoover, M.D., Sc.D., Director of the Epidemiology and Biostatistics Program, were asked to serve as an executive committee to support Dr. Tucker in her new role.
Many DCEG research findings have served as key evidence by expert panels that develop consensus reports as to whether specific exposures cause cancer, by regulatory agencies that establish permissible exposure levels, and by the medical community to change clinical practice. Over the years, DCEG has had a significant impact on public health through the use of its research by national and international organizations, including the International Agency for Research on Cancer (IARC), the National Toxicology Program’s Report on Carcinogens (ROC), the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), and the Occupational Safety and Health Administration (OSHA); various agencies dealing with radiation safety; and many professional societies. Selected landmark findings include the following.

**Smokeless Tobacco**

- The U.S. Cancer Mortality Atlas revealed a striking elevation of oral cancer rates among women in the rural south. In a case-control study conducted in North Carolina, an elevated risk was associated with long-term use of snuff among non-smokers, reaching 50-fold for tissues in direct contact with tobacco. The published report in the *New England Journal of Medicine* (Winn et al., 1981) stimulated congressional hearings that resulted in regulatory actions to control the advertising and labeling of smokeless tobacco and educational campaigns to reduce its use by young people.

**Radiation**


- DCEG developed statistical models to calculate the radiation-related probability of cancer causation, known as the NIH radioepidemiological tables (NIH, 1985, 2003), including an online interactive program (Kocher et al., 2008) used by the National Institute for Occupational Safety and Health and the Veterans Administration for adjudicating compensation claims.

- Reports of the potential health risks of exposure to radioactive I-131 fallout from above-ground nuclear testing in the 1950s and 1960s formed the basis of national educational campaigns (NCI, 1997; Gilbert et al., 1998).

- The quantification of lung cancer risks associated with occupational and residential exposures to radon were critical to informing the EPA action level for radon mitigation (Qiao et al., 1989; Lubin et al., 1990, 1997, 1998, 2004; Alavanja et al., 1994, 1999; Wang et al., 2002).

- The study of second primary tumors after childhood cancer demonstrated a radiation dose–related relationship for certain cancers, such as bone sarcoma and thyroid cancer (Tucker et al., 1987, 1991), which has led to efforts to decrease doses of radiotherapy in children.

Over the years, DCEG has had a significant impact on public health through the use of its research by national and international organizations, various agencies dealing with radiation safety, and many professional societies.
• The striking dose-related risk of radiation-related second cancers among children treated for retinoblastoma (Kleinerman et al., 2005) has altered medical practice to reduce radiation exposure and intensify second cancer screening.

• Quantification of the dose response for lung and breast cancers after radiation treatment of Hodgkin lymphoma (Tucker et al., 1988; Travis et al., 2002, 2003) influenced clinical standards to reduce radiation fields, lower exposures, and avoid smoking.

• The elevated risk of radiation-related solid cancers reported among bone marrow transplant recipients affected clinical practice by moving the conditioning regimens away from radiation and using chemotherapy-based regimens as an alternative (Curtis et al., 1997; Socie et al., 2000; Rizzo et al., 2009).

• Statistical models estimating the cancer risks associated with radiation exposure from computed tomography (CT) scans (Berrington de González et al., 2009) led to a requirement that makers of scanners used at NIH incorporate software to measure and track patients’ radiation doses over time, an improvement that is being adopted by other hospitals and imaging facilities.

• A professional education brochure was created in collaboration with the Society for Pediatric Radiology in efforts to minimize the level of radiation from CT scans to children (2002, 2009).

• Concern was heightened by a recent epidemiological finding of small but statistically increased risks of leukemia and brain tumors in the first decade after CT exposure in children (Pearce et al., 2012).

Ultraviolet Radiation

• Surveys of ground-level ultraviolet radiation in relation to time trends for melanoma and other skin cancers have provided EPA with the estimated prevalence of skin cancer in relation to projected increases in ozone depletion.

Electromagnetic Fields

• The finding that cell phone use did not increase risk of brain tumors affected FDA’s regulatory policies on radiofrequency radiation (Inskip et al., 2001).

• Lack of an increased risk for childhood leukemia associated with high residential magnetic fields formed the basis of judicial rulings in the United Kingdom and elsewhere on the potential health effects of these exposures (Linet et al., 1997).

Occupation

• The excess risk of respiratory cancer among copper smelter workers (Lee and Fraumeni, 1969) and nearby residents (Blot and Fraumeni, 1975) exposed to inorganic arsenic has led to IARC’s classification of airborne arsenic as a human carcinogen and to new OSHA exposure limits.
Epidemiologic studies have investigated possible cancer risks from water contaminants and have provided further confidence in the safety of fluoride in drinking water. The findings also informed the World Health Organization’s WHO Guidelines for Indoor Air Quality: Selected Pollutants.

Water Contaminants

- A study linking disinfection byproducts to bladder cancer risk (Cantor et al., 1987) stimulated EPA to lower the allowable maximum contaminant levels for trihalomethanes and haloacetic acids in drinking water.

- No epidemiologic evidence was found that fluoride in drinking water poses an elevated risk of cancer, as had been suggested by some previous reports. The finding was confirmed by expert panels convened in the United States, the United Kingdom, and other countries, providing further confidence in the safety of water fluoridation (Hoover et al., 1976).

Indoor Air Pollution

- Increased lung cancer associated with smoky coal use (Lan et al., 2002, 2008) and cooking fumes (Gao et al., 1987) in China were key to IARC’s classification of indoor emissions from household combustion of coal as an established human carcinogen and emissions from high-temperature frying as a probable human carcinogen.

- Excess lung cancer reported among chromium pigment workers (Hayes et al., 1989) was among the study findings that led to IARC’s classification of chromium compounds as carcinogenic.

- Studies showing increased nasal cancer among furniture workers (Brinton et al., 1977, 1984) influenced IARC’s classification of wood dust exposure as a human carcinogen.

- A report of increased lymphoma risk associated with 2,4-D exposure (Hoar et al., 1986) led to EPA label instructions to change clothes after application and influenced the Veterans Administration’s compensation policies for exposure to Agent Orange.

Formaldehyde, which is often found in plastic plates, formalin (used as a preservative), and plywood, is now classified as a human carcinogen.

- The increased occupational risks of bladder cancer (Silverman et al., 1983) and lung cancer (Silverman et al., 2012) led IARC to classify diesel exhaust fumes as an established human carcinogen.

- Elevated risks of nasopharyngeal cancer and leukemia among formaldehyde-exposed workers (Blair et al., 1986; Hauptmann et al., 2003, 2004, 2009; Beane Freeman et al., 2009) were key to IARC’s and ROC’s classifications of formaldehyde as a human carcinogen and led to EPA regulatory standards.

- Evidence of hematotoxicity from benzene exposure at levels below the occupational standard at the time (Lan et al., 2004) led to a lower action level in China and informed an EPA rule limiting the benzene content in gasoline and requiring controls on passenger vehicles and portable fuel containers to reduce pollutants.

- Studies of silica-exposed miners and workers in pottery factories and dusty trades (Chen et al., 1989, 1990, 1992; Amandus et al., 1991, 1995) were cited in IARC’s classification of silica as a human carcinogen.
Diet/Nutrition/Physical Activity

- The lack of an association between saccharin use and bladder cancer risk (Hoover and Strasser, 1980) was part of the evidence that prompted ROC to delist saccharin as a potential carcinogen.

- Several studies indicating that diets high in vegetables and fruits are associated with reduced risk of various cancers (Ziegler et al., 1981, 1986; Winn et al., 1984) influenced public health recommendations.

- The Nutrition Intervention Trials in Linxian, China, were the first randomized trials to demonstrate that vitamin/mineral supplementation reduces total and cancer mortality in a population with nutritional deficiencies (Blot et al., 1993).

- Studies of serum levels of vitamin D in relation to cancer mortality (Freedman et al., 2007) and breast cancer risk (Freedman et al., 2008) were key to the Institute of Medicine’s 2010 report Dietary Reference Intakes for Calcium and Vitamin D.

- Studies reporting an increased risk of pancreatic cancer associated with vitamin D intake (Stolzenberg-Solomon et al., 2006, 2009, 2010) have dampened enthusiasm for supplementing vitamin D above a physiologic dose.

- Reports that carcinogenic heterocyclic amines are generated in meat during high-temperature cooking (Sinha et al., 1994, 1995) led to public health recommendations on cooking practices.

- Studies indicating a reduced risk of colon, breast, endometrial, and ovarian cancers (Albanes et al., 1989; Chow et al., 1993; Dosemeci et al., 1993; Sturgeon et al., 1993; Zheng et al., 1993) were cited in the 1996 Surgeon General’s Report on Physical Activity and Health.

Pharmaceuticals and Medical Devices

- Long-term follow-up of cohorts exposed prenatally to diethylstilbestrol (DES) revealed a broader spectrum of adverse health outcomes than previously known. These findings have affected medical surveillance of exposed persons and have sparked research on the effects of early-life chemical exposures beyond DES (Hatch et al., 1998, 2001, 2011; Titus-Ernstoff et al., 2001, 2010; Troisi et al., 2007a, 2007b; Hoover et al., 2011).

- The finding that hormone replacement therapy is associated with increased breast cancer risk—and that the risk is greater with estrogen-progestin regimens than with estrogen alone (Hoover et al., 1976; Schairer et al., 2000)—has changed medical practice, resulting in a decrease in breast cancer incidence.

- Evidence against breast implants causing an increase in breast cancer or connective tissue disorders (Brinton et al., 2004, 2006) contributed to FDA’s decision to allow the devices back on the market.
Evidence that ovulation-stimulating agents do not significantly increase the risk of ovarian and other cancers (Brinton, Lamb et al., 2004; Brinton, Scoccia et al., 2004) has reduced concern about prescribing these increasingly popular drugs.

A study of leukemia after childhood cancer revealed a dose-response relationship with alkylating agent chemotherapy, after adjusting for radiation (Tucker et al., 1987), which led to decreased use of these agents for the treatment of childhood cancer.

A dose-response risk of childhood leukemia was seen following treatment with chloramphenicol (Shu et al., 1987). As a result of this and other evidence, chloramphenicol is no longer the first-line agent for any infection in developed countries.

A study of secondary leukemia after treatment of breast cancer affected clinical practice by demonstrating the substantial risk associated with melphalan and the relative safety of the current cyclophosphamide-based chemotherapy regimens (Curtis et al., 1992).

Quantification of the increased risks of lymphoma and certain other cancers associated with immunosuppressive drugs in transplant recipients (Hoover and Fraumeni, 1973) led to FDA warnings as well as screening recommendations.

Evidence showing an excess risk of leukemia among women treated with chlorambucil for ovarian cancer (Greene et al., 1982) was key to IARC’s classification of the drug as a human carcinogen and to FDA clinical alerts.

Infectious Agents

A study of newborns who were inadvertently given SV40-contaminated polio vaccine suggested no increased risk of cancer (Fraumeni et al., 1963; Fraumeni et al., 1970; Mortimer et al., 1981), thereby alleviating public health concerns about exposure to this oncogenic virus.

The increased risks of human T-cell leukemia virus type 1 (HTLV-I) and HTLV-I–associated myelopathy/tropical spastic paraparesis (HAM/TSP) found among persons infected with HTLV-I (Blattner et al., 1982; Blayney et al., 1983) were critical to FDA recommendations to screen blood donations for HTLV-I/II.

DCEG research provided the initial assessment of the specificity, sensitivity, and appropriate applications of the first-generation HIV antibody testing system for diagnosis of HIV infection (Weiss et al., 1985).

A prospective study of HIV infection and the development of AIDS in subjects with hemophilia showed that a much larger proportion of HIV-infected persons would develop AIDS than previously thought (Goedert et al., 1989), which had public health and clinical impact.

Recognition that CD4 count and HIV load predict risk for AIDS and death (Goedert et al., 1987, 1989; Ehmann et al., 1994; O’Brien et al., 1996) had clinical applications for screening and counseling.

A study of HIV infection among laboratory workers influenced new recommendations for handling HIV in the laboratory (Weiss et al., 1988).

New “back calculation” statistical methods were used to derive estimates of HIV prevalence by the U.S. Public Health Service and showed that the HIV prevalence was greatest among persons at risk through heterosexual contact (Rosenberg et al., 1991; Rosenberg, 1995; Rosenberg and Biggar, 1998).

Demonstration that serological tests for human herpesvirus 8 had poor reproducibility (Rabkin et al., 1998) contributed to FDA’s decision not to screen the U.S. blood supply.

Landmark studies of the natural history of cervical cancer firmly established human papillomavirus (HPV) as the necessary cause (Schiffman et al., 1993, 2007), laying the groundwork for vaccine and screening strategies.

The finding that one or two doses of an HPV 16/18 vaccine may prevent cervical cancer just as effectively as three doses is likely to lower the cost and encourage the global dissemination of the vaccine (Kreimer et al., 2011).
Studies into the benefits of incorporating HPV testing into cervical cancer screening programs (Katki et al., 2011) have informed screening guidelines issued by the U.S. Preventive Services Task Force, the American Cancer Society, the American Society for Clinical Pathology, and the American Society for Colposcopy and Cervical Pathology.

Studies linking *Helicobacter pylori* infection to the very high incidence of gastric cancer and precancerous lesions in Shandong province in China prompted a clinical trial that showed a sustained reduction in risk following a two-week course of antibiotics (You et al., 2006; Zhang et al., 2006; Ma et al., 2012).

Hereditary Syndromes

Identification of the inherited genes responsible for hereditary cancer syndromes and mutation carriers has had a significant impact on the clinical management of these and related conditions. Examples include the discovery of Li-Fraumeni syndrome and the role of *p53* (Li and Fraumeni, 1969, 1982; Li et al., 1988; Malkin et al., 1990) and the roles of *NF2* in neurofibromatosis type 2 (Rouleau et al., 1993; Trofatter et al., 1993); *CDKN2A*, *CDK4*, and *MITF* in hereditary melanoma (Hussussian et al., 1994; Zuo et al., 1996; Yokoyama et al., 2011); *PTCH* in nevoid basal cell carcinoma syndrome (Hahn et al., 1996); *SUFU* in medulloblastoma (Taylor et al., 2002); and *T* (brachyury) duplication in familial chordoma (Yang et al., 2009).

Detailed clinical studies of neurofibromatosis type 2 revealed heterogeneity of the disease phenotype, changed clinical management, and informed genetic counseling (Kaiser-Kupfer et al., 1989; Parry et al., 1994, 1996; Rutledge et al., 1996).

Studies of monoclonal B-cell lymphomatosis as a precursor condition for chronic lymphocytic leukemia (CLL) in high-risk families and in the general population have facilitated screening and early diagnosis of CLL (Landgren et al., 2009; Goldin et al., 2010).

The observations that patients with dyskeratosis congenita (DC) have extremely short telomeres and that approximately 60 percent have a germline mutation in a telomere biology gene led to the development of telomere length as a diagnostic test for DC and new criteria for evaluating potential bone marrow donors (Alter et al., 2007; Savage et al., 2008).

A novel chromosome 9q deletion in a patient with nevoid basal cell carcinoma syndrome followed by genetic linkage and fine-mapping studies led to the identification of the *PTCH* gene as the cause of this syndrome (Gailani et al., 1992; Hahn et al., 1996; Chidambaram et al., 1996). This work set in motion a research effort that recently culminated in the first...
FDA-approved biological agent (vismodegib) that targets the Hedgehog signaling pathway, a novel therapy for locally advanced and metastatic basal cell carcinoma of the skin.

- Publication of the *Concise Handbook of Familial Cancer Susceptibility Syndromes* has provided a useful reference for clinical recognition and management of these rare but important disorders (Lindor and Greene, 1998; Lindor et al., 2008).

**Breast Cancer**

- The Gail breast cancer risk assessment model (Gail et al., 1989) is widely used in risk prediction strategies, including FDA guidelines on the use of tamoxifen and raloxifene for breast cancer risk reduction.

- A study of *BRCA1* and *BRCA2* alterations in the Ashkenazi Jewish population of Washington, D.C., reported lower penetrance for breast and ovarian cancers than earlier studies in families with hereditary breast cancer. The findings highlighted the importance of population-specific founder mutations in genetic testing and affected the clinical management of carriers (Struewing et al., 1997).

- Studies in hereditary breast/ovarian cancer uncovered the value of risk-reducing salpingo-oophrectomy, now considered a standard-of-care treatment option in the management of women in high-risk families (Tobacman et al., 1982; Struewing et al., 1995; Kramer et al., 2005; Greene et al., 2008, 2011).

- Epidemiological studies using tumor tissue microarrays have revealed the heterogeneity of breast cancer in terms of risk factors and prognosis.

**Melanoma**

- Identification and characterization of dysplastic nevi as the major risk factor for melanoma informed the guidelines for melanoma screening and clinical management in high-risk families and in the general population (Reimer et al., 1978; Greene et al., 1985a, 1985b; Tucker et al., 1997).

- A clinical atlas depicting melanoma and precursor lesions, training videos to help health care providers examine high-risk families, and a risk calculator to estimate an individual’s probability of developing melanoma have been important milestones in managing this disease (Tucker et al., 2002; Fears et al., 2006).

For complete references cited in this article, visit http://dceg.cancer.gov/linkage-public-health-citations.

—Compiled by Shelia Hoar Zahm, Sc.D.
Among the numerous publications of Joseph F. Fraumeni, Jr., M.D., are several texts and reference volumes that have played a pivotal role in advancing and integrating cancer epidemiology and related fields. These publications include the following books:


Collaboration and Consortia

Collaboration is the hallmark of contemporary scientific research, as scientists form teams and partnerships to study complex, multifaceted problems. In epidemiology, the relatively small studies of 300 or fewer subjects that predominated before the mid-1980s would not have adequate statistical power to investigate the relatively low-level effects of risk factors that are of particular interest today. Under the leadership of Joseph F. Fraumeni, Jr., M.D., DCEG has partnered with NCI’s Division of Cancer Control and Population Sciences (DCCPS) to foster and support large-scale extramural-intramural consortial initiatives to assemble the substantial quantity of data and biospecimens necessary to conduct a wide range of epidemiologic studies.

An early example of “big science” involving extramural-intramural collaboration was the National Bladder Cancer Study, which DCEG launched in 1978 to examine the role of artificial sweeteners, notably saccharin, in the development of bladder cancer, a relationship suspected on the basis of laboratory animal studies. Because the expected risk was low, the investigators determined the need to enroll approximately 3,000 cases and 5,800 controls, about 10 times the size of a typical study of the era. Toward this end, DCEG investigators partnered with the Surveillance, Epidemiology and End Results (SEER) program to conduct a multicenter, population-based study. In addition to shedding light on the major public health concern about saccharin use, the study provided an opportunity to investigate the effects of a wider range of lifestyle, environmental, and occupational exposures on bladder cancer risk.

In recent decades, epidemiologic research has become increasingly interdisciplinary, especially with the advent of new genomic and molecular markers that have sharpened our measures of causal factors and mechanisms as well as diverse outcomes. Biomarkers of cancer susceptibility initially took the form of studies that evaluated the risk associated with candidate genes, which were underpowered and led to many positive findings that could not be reproduced. DCEG was well positioned to foster and participate in large-scale consortia involving case-control, cohort, and family studies, a strategy through which genetic findings could be identified with some precision and then replicated rapidly and efficiently.

In 2002, extramural and intramural leaders of case-control studies of non-Hodgkin lymphoma (NHL) formed the international “InterLymph Consortium” to investigate a number of candidate genes suspected to confer susceptibility (see Figure 1). The Consortium identified the TNF gene as playing a role in NHL and, just as importantly, it ruled out the IL1A gene as a meaningful contributor to risk. InterLymph has now grown to include consortia for genome-wide and other studies of Hodgkin lymphoma and multiple myeloma.

In 2003, the Breast and Prostate Cancer and Hormone-Related Gene Variant Study (BPC3) was launched to enable large-scale analyses of candidate genes that affect hormone metabolism. The NCI study combined the resources of two intramural cohorts and six extramural cohorts, with prospectively gathered prediagnostic plasma samples; lymphocytes; body measurements; and extensive questionnaire data on diet, physical activity, exogenous hormones, smoking, and other lifestyle factors from more than 740,000 men and women, including 8,850 with prostate...
There are many challenges in establishing large-scale interdisciplinary studies, but we need such strategies if we hope to more fully understand the biological mechanisms of cancer induction and progression and the means of preventing and controlling cancer.”

—Joseph Fraumeni

cancer and 6,160 with breast cancer. With the availability of high-throughput genomic and metabolic technologies for genome-wide association studies, the epidemiologic infrastructure has helped to unravel the role of genetic and hormonal risk factors for these tumors.

Family studies–based consortia also have been a focus for research on inherited mutations and cancer susceptibility. One of the earliest examples is the GenoMel Consortium, formed in 1997, in which DCEG joined forces with groups from more than 20 countries. The collaboration aims to identify and understand the genetic underpinnings of melanoma, including interactions with sun exposure and other risk factors, and their incorporation in risk-prediction models for individual patients.

Consortial strategies have more than proved the worth of large-scale collaborative research that incorporates innovative high-throughput technologies into robust epidemiologic designs to dissect the genetic and environmental components underpinning complex disorders such as cancer. NCI currently supports more than 50 consortia of various kinds. “Dr. Fraumeni recognized early on that for the kind of detective work it takes to unravel the complexities of cancer etiology, you need two things—teams of experts (because no one person can have all the expertise) and access to large numbers of study subjects and measurements of data so you can study the multiplicity of potential risk factors,” said Deborah M. Winn, Ph.D., Deputy Director of DCCPS. To date, the combined efforts of DCEG and DCCPS have led to dozens of epidemiologic consortia that are striving to inform clinical and public health interventions.

When asked to evaluate the future of collaborative studies in the era of molecular epidemiology, Dr. Fraumeni commented, “There are many challenges in establishing large-scale interdisciplinary studies, but we need such strategies if we hope to more fully understand the biological mechanisms of cancer induction and progression and the means of preventing and controlling cancer.”

—Patricia Hartge, Sc.D., and Wendy Schneider-Levinson
As DCEG Director, Joseph F. Fraumeni, Jr., M.D., recognized that the development of a strong research program requires attracting and training the next generation of scientists. Shortly after NCI established DCEG in 1995, Dr. Fraumeni created the DCEG Office of Education (OE) to oversee training and career development for various levels of scientific staff, coordinate the recruitment of postdoctoral fellows, develop and oversee predoctoral training partnerships with schools of public health, and establish and evaluate practices and policies. DCEG now provides unparalleled training for epidemiologists, biostatisticians, geneticists, clinicians, and laboratory scientists.

Dr. Fraumeni’s long-time mentor and colleague, Dr. Robert W. Miller, shaped Dr. Fraumeni’s perspective on training and development in epidemiology at an early stage. Dr. Miller became Chief of the Epidemiology Branch at NCI in 1961, one year before Dr. Fraumeni joined NCI as a commissioned officer in the U.S. Public Health Service.

“Bob was a marvelous mentor to all of us who joined his research program in positions equivalent to postdoctoral fellows,” said Dr. Fraumeni. “I believe I was his first and his longest serving protégé at NCI. He encouraged as much independence as we could handle, and he was generous in providing the guidance needed to pursue and complete our studies.”

In the early 1960s, the Epidemiology Branch was small. “In truth, epidemiologists in the United States devoted to cancer research were few and far between,” said Dr. Fraumeni. “Bob started from scratch to create an epidemiological research program with a strong clinical and interdisciplinary focus. He recruited and trained young physicians and scientists, many of whom have become leaders in the field.” Dr. Fraumeni soon followed in Dr. Miller’s footsteps, becoming a strong advocate for training within the NCI epidemiology research community.

DCEG’s fellowship training program has grown to more than 140 predoctoral and postdoctoral fellows. Predoctoral trainees include doctoral candidates, fellows who have obtained a master’s or baccalaureate degree, and summer students. Fellows comprise about one-third of DCEG’s workforce, and their contributions are vital to the Division’s research mission. DCEG maintains formal partnerships with the Yale University School of Public Health, the Johns Hopkins Bloomberg School of Public Health, and the George Washington University School of Public Health and Health Services. These partnerships have yielded talented scientists who have launched their careers based on the research they completed while at DCEG.

As leaders for training in the Division, Jackie Lavigne, Ph.D., M.P.H., Chief of OE, and Kristin Kiser, M.H.A., M.S., fellowship coordinator, provide personalized support and opportunities for professional growth to fellows and scientific staff. Having an office dedicated to training across the Division enables DCEG to offer its fellows the potential to work with and learn from experts in many aspects of cancer epidemiology and genetics through direct mentorship, workshops, courses, and lecture series. Under the guidance of dedicated, experienced mentors, DCEG fellows gain in-depth experience in designing and executing research studies, analyzing data, and interpreting and publishing the results. Evidence of the success of trainees in the DCEG environment lies in their record of publishing the results of their innovative and high-quality research. Current and recent DCEG fellows are often the lead authors of papers published in the top scientific and medical journals.
DCEG also offers a variety of practical opportunities for fellows to develop a comprehensive set of professional skills, including giving research presentations (at local, national, and international meetings), planning scientific events, mentoring, and writing grant proposals. The Division provides a wide range of supplemental courses in such fields as molecular epidemiology, genetic analysis, radiation epidemiology, and dosimetry. Several DCEG lecture programs are available for fellows and staff, including the Visiting Scholars Program, the Distinguished Lecturer Series, and the weekly DCEG Seminar Series. Fellows have the opportunity to participate in many other activities, such as the Fellows Monthly Colloquia, Career Development Seminars, the annual DCEG Fellows’ Training Symposium, and a variety of Institute and NIH meetings.

In June 2011, the North American Congress of Epidemiology recognized DCEG’s commitment to training by giving the Division the inaugural Alexander D. Langmuir Award for Training Program Excellence and Innovation. The award recognizes outstanding training programs in epidemiology that emphasize research experience and skills development, the application of epidemiology principles and advanced methods, and the importance of collaborative and integrative epidemiologic approaches. Dr. Lavigne accepted the award on behalf of DCEG during a ceremony at the Third North American Congress of Epidemiology in Montreal, Canada.

NCI has not tracked the number of people who have received training in epidemiology since Dr. Fraumeni arrived at the Institute in 1962. However, since NCI established DCEG in 1995, the Division has trained more than 600 outstanding cancer epidemiologists, many of whom are actively involved in epidemiology research in the United States and various other countries around the world. DCEG trainees are now working in academia, cancer centers and hospitals, federal and state government agencies, nonprofit organizations, and the private sector.

DCEG will continue to move forward, supporting and expanding Dr. Fraumeni’s vision of training the next generation of cancer epidemiologists, biostatisticians, geneticists, and others by providing them with experience in evolving interdisciplinary research to meet the scientific challenges that lie ahead.

—Victoria A. Fisher, M.P.H., and Jackie Lavigne, Ph.D., M.P.H.
In May, DCEG was privileged to hold a panel discussion titled Cancer Epidemiology over the Last Half-century and Thoughts on the Future. The panel featured Joseph F. Fraumeni, Jr., M.D., and Dr. David Schottenfeld, University of Michigan, co-editors of multiple editions of the indispensable textbook Cancer Epidemiology and Prevention. Robert N. Hoover, M.D., Sc.D., Director of DCEG’s Epidemiology and Biostatistics Program, moderated the discussion and posed questions on the major influences that affected the careers of Drs. Fraumeni and Schottenfeld, the key contributors and seminal discoveries in the field of cancer epidemiology, and advice for young epidemiologists. The full-capacity audience of NCI staff thoroughly enjoyed the panel members’ thoughtful, gracious, enlightening, and often humorous responses.

Both Drs. Fraumeni and Schottenfeld initially had trained as clinicians, but influential mentors steered them toward careers in epidemiology. Dr. Schottenfeld was in his second year in the Epidemic Intelligence Service at the Centers for Disease Control and Prevention when he was assigned to work with Dr. Abraham Lilienfeld at the Johns Hopkins School of Hygiene and Public Health on a multi-hospital case-control study of male breast cancer. Dr. Schottenfeld recalled, “When I went to Hopkins, the chemistry with Abe Lilienfeld was perfect. On completing the project, I was persuaded to abandon my notion about being a practicing oncologist but instead pursue a career in cancer epidemiology and public health. The relationship that we developed was sustained throughout my career.”

Similarly, Dr. Fraumeni was encouraged to go into epidemiology by Dr. Rulon Rawson, chairman of the Department of Medicine at the Memorial Sloan-Kettering Cancer Center, where Dr. Fraumeni served as chief resident.

When asked to identify the cancer epidemiologists who have had the most significant impact on the field, Drs. Fraumeni and Schottenfeld agreed that the towering figure in cancer epidemiology, and epidemiology in general, was Sir Richard Doll at Oxford University in the United Kingdom. Professor Doll, along with Dr. Ernst Wynder in the United States, was the first to establish a causal relationship between cigarette smoking and lung cancer. However, Professor Doll’s contributions to epidemiology extended well beyond that landmark finding.

Dr. Fraumeni also cited Mr. William Haenszel, former Chief of NCI’s Biometry Branch, whose landmark studies of the changing cancer risks among migrant populations offered many key epidemiologic insights; Dr. Miller for his trailblazing work in clinical epidemiology and childhood cancer; and Dr. Alfred Knudson for his seminal contributions to cancer genetics. Dr. Schottenfeld also gave tribute to Sir Austin Bradford Hill. “His book Principles of Medical Statistics had an enormous impact on the medical profession, which tended not to think numerically or quantitatively,”
Dr. Schottenfeld explained. He also credited other biostatisticians who have made important and lasting contributions by developing rigorous study methods and analytical approaches in epidemiology. They included Mr. Nathan Mantel, Mr. Jerome Cornfield, Dr. Norman Breslow, Mr. Nicholas Day, Dr. Kenneth Rothman, and Dr. Sander Greenland.

After describing the dominant influence of tobacco in cancer etiology, Dr. Fraumeni spoke about the changing themes that motivated epidemiologic research over time, such as the possible role of viral infections during the 1960s; environmental and occupational hazards during the 1970s; dietary practices, including fat intake, in the 1980s; and genetics from the 1990s on. For epidemiology, the genomics era began with family-based studies of rare, high-penetrant genes and vastly expanded as new technologies enabled genome-wide association studies to identify common low-penetrant genetic variants at the population level. Dr. Schottenfeld cited several remarkable discoveries in epidemiology that were transformative in nature, such as the roles of human papillomaviruses in cervical cancer, hepatitis B and C in liver cancer, asbestos exposure in lung cancer and mesothelioma, ionizing radiation in a wide variety of cancers, and the detection of low-level risks of lung cancer associated with passive smoking.

Drs. Fraumeni and Schottenfeld also discussed epidemiologic discoveries that were surprising at the time and caused paradigm shifts in thinking about cancer etiology. Among their examples were the association of *Helicobacter pylori* infection with duodenal ulcer and gastric cancer; the complex and varied effects of steroid hormones on the risk of breast and other cancers; the protective effects of aspirin on colon cancer risk; the discovery of vaginal adenocarcinomas in the daughters of women treated with diethylstilbestrol during pregnancy, which called attention to the potential importance of early-life exposures for cancer etiology; and the growing evidence that obesity increases the risk of several forms of cancer.

When asked about notable “characters” in cancer epidemiology and what made them so interesting, Drs. Fraumeni and Schottenfeld agreed that Dr. Wynder was the most colorful. Dr. Schottenfeld described him as “dramatic, flamboyant, charismatic, and, at times, infuriating. He had endless ideas. The only issue was that you had to pursue them. But he was enormously productive with hundreds of important publications.” Dr. Fraumeni remarked that Dr. Wynder combined a very active professional and social life, recalling a dramatic moment at the Memorial Sloan-Kettering Cancer Center when Dr. Wynder strolled into the cafeteria with the movie star Kim Novak.

After commenting on non-epidemiologists who had a positive effect on the field and discussing what they considered to be their own personal successes, Drs. Fraumeni and Schottenfeld turned the discussion to the importance of training the next generation of scientists, a career-long passion for both men. Dr. Schottenfeld exhorted young investigators, “You are going to have to be life-long students. You must continue to learn and continue to master your methodologies. You need to experience passion and joy in the research or else don’t trouble yourselves with all the years of competing for funding. You need to be questioning, to be critical observers, to think ‘out of the box’ in imaginative ways about questions, because it is framing the questions that’s the important issue.” Dr. Fraumeni encouraged young investigators to find the best possible mentors, work with compatible collaborators who have complementary skills, and carve out a niche in which to grow and eventually become an authority on the subject.

Drs. Fraumeni and Schottenfeld agreed that with imagination and resources, investigators should seize the opportunities to discover and investigate “natural experiments,” especially in the form of high-risk populations that provide etiologic clues. They also encouraged participation in large-scale collaborations and consortia when team science is warranted. Dr. Fraumeni concluded, “Despite the fact that we know so much more than we did 50 years ago, there is still an enormous amount that remains to be learned, and the opportunities in cancer epidemiology are greater than ever.”

*The video of the panel discussion is available at http://dceg.cancer.gov/fraumeni-schottenfeld-video.*

—Shelia Hoar Zahm, Sc.D., and Saloni Nayar, M.P.H.
Under the leadership of Joseph Fraumeni, DCEG has evolved from a small group of scientists to a world-class research organization.

DCEG staff members gathered in September 2012 to salute Dr. Fraumeni as he stepped down as DCEG Director.