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Biospecimens: Advancing Epidemiologic Research

Although the concept of biospecimen repositories, or biobanks, has been known for some time, recent advances in genomics, proteomics, and other technologies have underscored the growing importance of using biospecimens to advance biomedical research.

The availability of biospecimens is critical to epidemiologic research for identifying, developing, and validating biomarkers for cancer susceptibility, precursor states, carcinogenic exposures, and cancer progression and recurrence. "The advent of molecular epidemiologic research, including genome-wide association studies (GWAS), has highlighted the importance of incorporating biospecimens into epidemiologic strategies designed to identify the causes of cancers and the means of their prevention," stated **Joseph F. Fraumeni, Jr., M.D.,** Division Director. Biomarkers hold the key to studies of molecular pathways that lead to cancer development and progression; surrogate markers for drug efficacy and toxicity; and targets for cancer prevention, diagnosis, and treatment. Emerging new fields, such as metabolomics and microbiomics, also benefit from these discoveries.

As **Robert N. Hoover, M.D., Sc.D.,** Director of the Epidemiology and Biostatistics Program, explained, "Biospecimens are an important resource for studies of both

The Wedgewood Biorepository in Frederick, Maryland. *(Photo Credit: Fisher BioServices)*

DCEG *Linkage*

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cancer etiology and early detection by providing insights into the actual mechanisms of human carcinogenesis. They allow us to avoid some of the traditional challenges of 'conventional' epidemiology, which relies entirely on questionnaire data to measure variables of exposure and susceptibility." For example, beta-carotene intake can be directly measured from blood samples, rather than estimated based on a person's recollection of his or her usual dietary practices. The same holds true for measuring chemical exposures that may occur without an individual's knowledge, such as polychlorinated biphenyls, which have been implicated in liver cancer and lymphoma.

The availability of biospecimens has also allowed the discovery of biologic changes that precede cancer development. For example, an increased level of DNA damage in circulating lymphocytes may be a marker for an increased risk of lymphoid malignancies. "Studying biomarkers of disease allows us to better identify the causes of cancer," Dr. Hoover said. "Investigating events that occur closer to the time of an exposure can provide important etiologic clues long before the cancer itself develops."

Molecular epidemiology represents a strategy to probe into the nature of an epidemiologic association—such as the relation of obesity to breast cancer risk—by helping to elucidate the mechanisms involved. "Analysis of biospecimens has allowed us to implicate circulating estrogen levels in obese postmenopausal women as a likely mechanism for the increased breast cancer risk," Dr. Hoover said.

Studies differ in the types of specimens and the timing of sample collection. Most studies collect specimens at only one point in time. Others, such as the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, which contains about 2.9 million specimens in its repository, have multiple specimens collected at different points during the follow-up period. These serial specimens allow researchers to correlate changes in the activity of certain molecules with the onset of different types of disease. "Most studies have only one blood sample, and a few have two or possibly three samples," Dr. Hoover explained. "The availability of multiple blood specimens in PLCO provides a rare and an extremely valuable resource for studies of cancer etiology as well as early detection."

Traditionally, the search for early markers of cancer development has involved comparing people with cancer to those without it and examining the differences. Once a possible marker is found, it is then applied to a test population to see how well it identifies people with early-stage disease compared with those who remain disease-free. "PLCO is an ideal resource for these tests," Dr. Hoover said. "It's extremely advantageous when a researcher wants samples from people at least a year prior to a clinical cancer diagnosis, for example. If the biomarker predicts disease in that group, then you know you have a robust marker for early-stage disease. This greatly improves the outcomes of therapy."

DCEG's extensive biospecimen collection now includes nearly 12 million specimens, triple the number from just 10 years ago. The collection—stored in freezers at NCI-Frederick—includes a wide variety of specimens, such as blood, urine, and tissue, as well as DNA, RNA, and proteins extracted from many of those samples. Investigators may gain access to many of these biospecimens through a peer-reviewed application process.

Karen E. Pitt, Ph.D., DCEG special assistant for biological resources, oversees the Division's biospecimen collection and actively looks for ways to improve the way DCEG processes, stores, and tracks its biospecimens. Steps are taken to ensure that DCEG's biorepositories meet all standards and guidelines for collecting, handling, and storing biospecimens as established by the International Society for Biological and Environmental Repositories and the NCI Office of Biorepositories and Biospecimen Research. The Division's biospecimens are tracked using the Biospecimen Inventory Processing System (BSI-II), which stores information on each specimen as well as any modifications made to it over time. Many large projects have web portals that describe study specimens and the application procedures required for gaining access to them.

For the past two years, Dr. Pitt has been working with DCEG investigators, repository contract staff, and others to evaluate state-of-the-art equipment for specimen storage and handling, including increased use of robotics and automation to minimize contamination, enhance quality, and accelerate specimen handling. She and her colleagues have identified new equipment that will process samples more rapidly, improve the characterization of specimens, reduce labor and overall storage costs, and increase energy efficiency. To conserve valuable specimens, she has explored new techniques that permit biomarker assays requiring only minute quantities of samples. She also led efforts to establish a new DNA staging laboratory dedicated to preparing biological samples for genomic analysis.

Recently, Congress requested that NIH describe the methods used by the Intramural Research Program to track and store human biospecimens. **Shelia Hoar Zahm, Sc.D.,** DCEG Deputy Director, served as cochair of the NIH Scientific Directors Subcommittee on Biorepository Practices and Guidelines. She played an integral role in developing the "Guidelines for Human Biospecimen Storage and Tracking within the NIH Intramural Research Program" and led efforts to develop a legislative implementation action plan to address the new congressional reporting requirements related to human biospecimen storage. "Congress has asked NIH how it tracks its samples," Dr. Zahm said. "We greatly value the details of a good inventory system and the agreements that document how biospecimens can be used when they are transported to or from NIH."

Robert Hoover and Karen Pitt

Careful handling and documentation of specimens have greatly accelerated DCEG's research program in molecular epidemiology. These efforts are augmented by NCI's Applied Molecular Pathology Laboratory, which carries out high-throughput studies of gene expression and somatic mutations in tumor specimens collected as part of GWAS. The high-throughput construction of tissue microarrays enables the molecular subclassification of cancers and allows differential evaluation of risk factors for a variety of tumor subtypes. The approach also serves to link genomic and molecular alterations within tumors with the germline variants uncovered by GWAS and more fully illuminates the carcinogenic process in tumor induction and progression. These efforts are designed to catalyze downstream biological research and speed the translation of genomic discoveries into clinical practice while strengthening NCI's multidisciplinary research and training programs in cancer genetics and biology. ■

—Catherine B. McClave, M.S.

THREE TENURE-TRACK INVESTIGATORS JOIN IIB

DCEG's Infections and Immunoepidemiology Branch (IIB), formerly known as the Viral Epidemiology Branch, seeks to examine the important role of viral and bacterial infections as well as immunologic and inflammatory processes in cancer etiology. To expand IIB's research portfolio in these areas, three new tenure-track investigators joined the Branch in 2008.

Anil K. Chaturvedi, D.V.M., Ph.D., came to IIB as a postdoctoral fellow in 2005. He received his D.V.M. in 1999 from Andhra Pradesh Agricultural University in India and his M.P.H. and Ph.D. in epidemiology from Tulane University. Dr. Chaturvedi focuses his research on elucidating the role of infectious agents and immunologic alterations in cancer etiology, with a particular concentration on cancers of the lung and of the head and neck as well as AIDS-related cancers.

Dr. Chaturvedi has sought to gain a better understanding of the proportion of head and neck cancers attributable to human papillomavirus (HPV) infection and of the interactive effects among HPV, alcohol consumption, tobacco use, and oral hygiene. To address these questions, Dr. Chaturvedi is focusing his studies on populations in India, which has a very high incidence of head and neck cancers. Dr. Chaturvedi hopes his work will help improve secondary preventive measures, including screening and early detection. He explained that "the oral cavity is very amenable to both visual inspection and specimen collection, providing a unique opportunity for early detection of disease."

The research findings described in a paper by Dr. Chaturvedi and colleagues on HPV-associated head and neck cancers were selected as being among the *Journal of Clinical Oncology*'s major cancer research advances of 2008. The report showed a 0.8 percent increase in incidence per year from 1973 to 2004 for head and neck cancer sites related to HPV; conversely, the incidence of HPV-unrelated cancer sites was stable from 1973 to 1982 and decreased thereafter. Dr. Chaturvedi hypothesizes that changes in sexual behaviors among recent birth cohorts may explain the rising incidence of HPV-related head and neck cancers.


Anil Chaturvedi

Dr. Chaturvedi is also investigating the role of infections and inflammation in lung cancer. His studies in high-risk populations, such as HIV-infected individuals and survivors of cervical cancer, have recorded an increased risk of lung cancer that is not fully explained by smoking. To pursue these hypotheses, he is using the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial cohort to investigate the association between risk of lung cancer and chronic pulmonary infections, serum markers of inflammation, and genetic polymorphisms in the innate immunity and inflammation pathways. Dr. Chaturvedi is expanding his investigations by using a large multiplex panel of cytokines to better characterize the mechanisms involved.

His work also aims to characterize the relationship between HIV-induced immunosuppression and the increased risk of HPV-associated cancers. "Understanding this relationship is particularly relevant in the era of highly active antiretroviral therapies (HAART)," Dr. Chaturvedi stated. "As HIV-infected individuals live longer, the incidence of cancers that are not strongly related to immunosuppression may actually increase." Using the HIV/AIDS-Cancer Match Study, he recently showed that the incidence of anal cancers has increased significantly in the United States since the introduction of HAART in 1996.

Dr. Chaturvedi noted that "the significant advances in molecular epidemiology over the past several years have greatly enabled the study of infections, inflammation, and immunity in cancer etiology." Dr. Chaturvedi believes these studies have great relevance for prevention because the exposures are modifiable, as illustrated by the success of HPV vaccination programs.

Aimee R. Kreimer, Ph.D., joined IIB to pursue her interests in the epidemiology of HPV infection and cancers at cervical and non-cervical anatomic sites. She received her Ph.D. in infectious disease epidemiology from the Johns Hopkins Bloomberg School of Public Health in 2003, where she helped design and implement a case-control study that implicated HPV in the development of oropharyngeal cancer. An article about this study was recently published in the *New England Journal of Medicine*. For her postdoctoral research, Dr. Kreimer worked at NCI and the International Agency for Research on Cancer in Lyon, France, on studies of HPV-related cancers of the head and neck. When offered a tenure-track position within the Division, she knew it was a prime opportunity. "The resources, collaborations, and expertise across DCEG


Aimee Kreimer

place it at the forefront of HPV-related cancer research," Dr. Kreimer said.

At NCI, Dr. Kreimer has expanded her HPV research to include studies of esophageal, cervical, vulvar/vaginal, and anal cancers. Although HPV is generally linked to cervical cancer, there is mounting evidence that this virus may be associated with other cancers as well. "It was quite natural to begin studying HPV associated with cervical cancer because the model of HPV carcinogenesis at the cervix can be used to inform similar research at other sites in the body," she remarked.

Dr. Kreimer is actively involved in determining the efficacy of the HPV vaccine at both the cervix and non-cervical sites and in understanding the natural history of HPV infection through research conducted in NCI's HPV vaccine trial in Costa Rica. To date, the trial has followed 7,500 women for four years; six years will be added to the trial to collect data on the longer-term efficacy and impact of the vaccine.

Dr. Kreimer is also collaborating with extramural investigators on a prospective study of HPV infection in a cohort of cancer-free men. The men will be followed for five years, and specimens will be collected every six months to test for HPV infections and outcomes, including infections of the oral cavity. "Currently, we do not have a clear understanding of HPV infections among healthy individuals," Dr. Kreimer explained. "Obtaining data from multiple points in time will help to better understand the natural history of oral HPV infection."

Dr. Kreimer believes that the discovery of virus-related cancers affords an important opportunity for cancer prevention. "HPV vaccination provides an incredible opportunity to protect against some cancers for which screening and treatment are not available in most of the world," she said. "And if the vaccine is effective at protecting against extra-cervical infections, we may be able to further expand the scope of vaccination to protect against even more cancers."

Mahboobeh Safaeian, Ph.D. (IIB), began her work in the Division as a Sallie Rosen Kaplan postdoctoral fellow in the Hormonal and Reproductive Epidemiology Branch. She received her Ph.D. in epidemiology in 2006 from the Johns Hopkins Bloomberg School of Public Health, where her doctoral dissertation focused on innovative methods of screening for cervical cancer in resource-poor communities and in communities that resist pelvic examination. She explained, "There is a huge disparity in cervical cancer incidence and mortality between developed and developing countries, which is mainly attributed


Mahboobeh Safaeian

WORKSHOP EXPLORES LOW-DOSE RADIATION EPIDEMIOLOGY

In December, DCEG investigators participated in the workshop "Low dose radiation epidemiology: What can it tell us?" held in Bethesda. The workshop was sponsored by the Office of Science in the U.S. Department of Energy (DOE) and organized by Dr. Scott Davis of the University of Washington, Dr. Eric Hall of Columbia University, Dr. Noelle Metting of DOE, Dr. Jerome Puskin of the Environmental Protection Agency, and **Elaine Ron, Ph.D., M.P.H.,** Radiation Epidemiology Branch (REB). The goal of the workshop was to discuss the value of current epidemiologic data in learning about cancer and other health risks among populations exposed to low-dose or low-dose–rate radiation.

On the first day, investigators summarized relevant epidemiologic studies. **Kiyohiko Mabuchi, M.D., Dr.P.H.** (REB), and Dr. Dale Preston of Hirosoft International Corporation presented recent data from the Life Span Study of atomic bomb survivors in Japan; **Martha S. Linet, M.D., M.P.H.** (Chief of REB), and **Alice J. Sigurdson, Ph.D.** (REB), summarized data from a large cohort of U.S. radiological technologists exposed to occupational radiation; Dr. Ron, **Amy Berrington de Gonzalez, D.Phil.** (REB), and Dr. David Brenner of Columbia University discussed the large ongoing cohort study of cancer risk among children receiving computed tomography scans in the United Kingdom and efforts to conduct similar studies in other parts of the world; Dr. Preston, **Ethel S. Gilbert, Ph.D.** (REB), and Dr. Ron described ongoing research on health effects related to internal and external radiation exposure among Mayak nuclear workers in Russia; and Dr. Gilbert and others discussed the International Agency for Research on Cancer's 15-country study of nuclear workers. Additional presentations covered studies among a cohort of people exposed to environmental radiation from the Techa River in the Southern Urals, Russia; data from the U.S. Shipyard Worker study; and current investigations of the large DOE workforce of radiation workers. The final session of the day was devoted to studies of man-made and natural areas of high-background radiation.

On the second day of the workshop, **Jay H. Lubin, Ph.D.,** Biostatistics Branch, and REB investigators **Parveen Bhatti, Ph.D., M.S., Charles E. Land, Ph.D.,** and Drs. Gilbert, Linet, Mabuchi, Ron, and Sigurdson participated in panels discussing what could be learned from ongoing studies, the value of updating or expanding current studies, the possible need for new studies, the potential gain from pooling existing studies, and the integration of molecular technologies in epidemiologic studies.

—Elaine Ron, Ph.D., M.P.H.

to lack of resources for screening and, in some countries, reluctance among asymptomatic women to seek a pelvic exam. It was very exciting to have had the opportunity to validate HPV assessment in self-collected vaginal samples, which paves the way for much-needed research in countries and settings where cervical disease is a major public health problem."

Researchers do not yet know why the majority of women with HPV infections eventually clear the infection while others go on to develop cervical cancer. To explore this issue, Dr. Safaeian is evaluating the role of cofactors in the progression of HPV infection through studies of inflammatory mechanisms, immune response, and genetic factors.

"The unique opportunity to partner with Dr. Ligia Pinto and her colleagues at the HPV Immunology Laboratory at NCI-Frederick, along with access to the HPV-related cohort studies in the Division, has allowed me to efficiently evaluate and utilize assays that measure the inflammatory and immunologic pathways attributable to HPV-related cancer," Dr. Safaeian said.

To investigate the contribution of coinfection and inflammatory processes to the development of cervical cancer, Dr. Safaeian is studying the role of *Chlamydia trachomatis* in cervical carcinogenesis among HPV-infected women in the HPV Natural History Study in Costa Rica. Because *C. trachomatis* and HPV infection have similar risk factors, special efforts are being made to determine whether *C. trachomatis* contributes independently to cervical carcinogenesis among HPV-positive women or whether the association is the result of residual confounding.

The progression of cervical cancer is affected by the type of HPV infection. To further investigate this association, Dr. Safaeian is comparing oncogenes in HPV types 16 (which accounts for nearly half of all cervical cancer), 31 (moderately associated with cervical cancer), and 73 (not associated with cervical cancer) to determine whether genetic and functional differences in HPV-16 may explain how it uniquely contributes to cervical cancer.

Dr. Safaeian is also studying differences in immune response to HPV infection and vaccination to determine whether the immune system's reaction to HPV exposure contributes to the risk of subsequent HPV infections and cervical carcinogenesis. Within cohorts established by the Division, Dr. Safaeian is analyzing natural seropositivity to determine whether previous infections with an HPV type protect against future infections when a woman is re-exposed to the same or a similar HPV type. She is also investigating whether vaccinated women in the Costa Rica trial are partially protected against HPV infections of related types and the reasons for vaccine failure against these related types. In addition, she is evaluating host genetic markers associated with persistent infection and disease progression. Through these studies, Dr. Safaeian seeks to gain a deeper understanding of host factors that may help explain why some HPV-positive women develop cervical cancer while others do not. She hopes these studies will provide insights into the role of immune response in carcinogenesis at other sites. ■

—Jennifer Monti

FALL 2008 INTRAMURAL RESEARCH AWARD WINNERS

DCEG Intramural Research Awards (IRAs) are competitive funding opportunities designed to encourage innovative, interdisciplinary research by Division fellows and tenure-track scientists. The IRA program includes spring and fall cycles with as many as three proposals awarded at up to $50,000 each.

IRA Winners: Laufey Amundadottir, Nicolas Wentzensen, and Jonine Figueroa.

After a vigorous competition, three winners have been announced for fall 2008. They are **Laufey Amundadottir, Ph.D.,** Laboratory of Translational Genomics, for her proposal "High-resolution epigenetic annotation of susceptibility loci from breast, prostate, and pancreatic cancer genome-wide association studies"; **Jonine D. Figueroa, Ph.D., M.P.H.,** Hormonal and Reproductive Epidemiology Branch (HREB), for "Breast cancer risk factors and markers of proliferation, apoptosis, and hormone receptor expression in normal breast biopsies"; and **Nicolas Wentzensen, M.D., Ph.D.** (HREB), for his project on "Methylation profiling of ovarian and endometrial cancers: Development of a marker panel for studies of etiologic heterogeneity and early detection."

Proposals were reviewed by members of the NCI Board of Scientific Counselors and senior DCEG scientists and were judged on their potential for significant scientific and public health impact, innovation, interdisciplinary nature, ability to achieve the objectives within the proposed time frame and resources, and relevance to the mission of the Division and Institute.

PRESIDENT'S CANCER PANEL TACKLES ENVIRONMENTAL FACTORS

During the past year, the President's Cancer Panel held a series of meetings to carefully review the scientific evidence, advances, and barriers to progress pertaining to environmental factors in cancer. In doing so, the panel called on the expertise of a number of DCEG investigators.

Speakers: Jay Lubin, Mary Ward, Kenneth Cantor, Martha Linet, Laura Beane-Freeman, and Michael Alavanja.

As Dr. Abby B. Sandler, Chief of the NCI Institute Review Office and Executive Secretary of the President's Cancer Panel, explained, "Each year, the panel looks at a different aspect of cancer, reviews the scientific evidence, and reports back to the President." When the panel decided to look at environmental factors, "We naturally turned to the world's experts on these topics here in the Division of Cancer Epidemiology and Genetics."

"A number of people in the Division were hugely helpful in organizing this series," Dr. Sandler noted. These included DCEG Deputy Director **Shelia Hoar Zahm, Sc.D.; Aaron E. Blair, Ph.D., M.P.H.,** Scientist Emeritus in the Occupational and Environmental Epidemiology Branch (OEEB); and **Martha S. Linet, M.D., M.P.H.,** Chief of the Radiation Epidemiology Branch.

The Environmental Factors in Cancer series included four public meetings, with DCEG investigators presenting at three of the sessions. In October, **Michael C.R. Alavanja, Dr.P.H.** (OEEB), spoke on cancer in agricultural populations and the growing evidence linking specific agricultural exposures to specific cancers. He was joined by **Laura Beane-Freeman, Ph.D.** (OEEB), who spoke on the Agricultural Health Study and the Agricultural Cohort Consortium, and **Mary H. Ward, Ph.D.** (OEEB), who spoke on human exposure to nitrogen fertilizers, primarily through drinking contaminated water, and discussed evidence linking such exposure to cancer.

Jay H. Lubin, Ph.D., Biostatistics Branch, and **Kenneth P. Cantor, Ph.D., M.P.H.** (OEEB), participated in a December meeting devoted to the effects of air pollution and water contamination. Dr. Lubin presented wide-ranging evidence that radon exposure is a human lung carcinogen, including findings from cohort studies of radon-exposed underground miners and case-control studies of residential radon. Dr. Cantor gave an overview of the epidemiologic evidence for the effects of carcinogens in drinking water, particularly inorganic arsenic and byproducts of chlorine used to disinfect water, but also including nitrates, radionuclides, and various organic and inorganic chemicals.

Dr. Linet participated in the fourth and final meeting in January on radiation exposures. Her presentation, "Cellular telephone use and cancer risk," related brain cancer incidence to trends in cell phone use by looking at biological effects of radiofrequency radiation, early epidemiological studies, more recent investigations and pooled analyses of several central nervous system tumors, and data from occupational studies. Dr. Linet summarized the strengths and limitations of epidemiological investigations to date and identified gaps in knowledge.

The President's Cancer Panel formally dates from 1971, when it was created by Section 407 of P.L. 92-218, the "War on Cancer" Act, to monitor the development and execution of the National Cancer Program. It has a mandate to report directly to the President.

Dr. Sandler summed up DCEG's participation in this important endeavor: "They were very supportive and enthusiastic. These were clearly the people to turn to." ■

—Terry Taylor, M.A.

STUDY TO UNDERSTAND CERVICAL CANCER

In November 2003, the Study to Understand Cervical Cancer Early Endpoints and Determinants (SUCCEED) was launched to increase understanding of the mechanisms involved in the progression of human papillomavirus (HPV) infection to cervical cancer and to develop a new set of biomarkers that can better distinguish those women at highest risk of developing cervical cancer from those with benign infections. Principal investigator **Sophia S. Wang, Ph.D.,** Infections and Immunoepidemiology Branch (IIB), **Mark E. Sherman, M.D.,** Hormonal and Reproductive Epidemiology Branch (HREB), **Nicolas Wentzensen, M.D., Ph.D.** (HREB), **Jill Koshiol, Ph.D.** (IIB), **Mahboobeh Safaeian, Ph.D.** (IIB), **Sholom Wacholder, Ph.D.,** Biostatistics Branch, and **Mark Schiffman, M.D., M.P.H.** (HREB), are working in collaboration with the Oklahoma University Health Sciences Center (OUHSC) on this large cross-sectional study.

Although HPV infection may lead to the development of cervical cancer, the majority of women with HPV infections will not develop cancer, and many may never even develop cervical abnormalities. The major analytic goal of SUCCEED is to better understand cervical carcinogenesis by studying the distinctive molecular events that occur in the cervix and incorporating epidemiological, clinical, pathologic, and molecular biologic data from women with various stages of HPV infections (i.e., normal, HPV-infected, precancer, cancer).

Data collected in SUCCEED include a large set of frozen tissue samples, spanning the spectrum of cervical pathogenesis, from nearly 2,000 women who were referred for colposcopy at OUHSC.

SUCCEED study components	
Questionnaire data	Gynecologic, sexual, reproductive, medical, sexually transmitted disease, and behavioral (e.g., smoking) history
Tissues Biopsies	Snap frozen lesional tissue (mRNA, DNA)
Loop electrosurgical excision procedure	Snap frozen lesional tissue (mRNA, DNA)
	Snap frozen "normal" tissue (mRNA, DNA)
Paraffin-embedded tissues	Retained for immunostaining and validation efforts
Blood (10 mL)	Serum for immune marker measurements or other uses
	Clots for DNA extraction
Cervical cells	Aliquot (pellet) archived
	Cytology—stained slide for cytology diagnosis
	Archived in RNA-friendly medium
	Aliquot for HPV typing (37 types)
	Cytology—unstained slide in gaseous nitrogen for biomarker validation
Cervical secretions	Frozen for immune measurements

Figure 1. Summary of data and biospecimens collected in SUCCEED.

In addition, blood samples and cervical secretions, along with data on medical and behavioral HPV cofactors known to be associated with cervical neoplasia, were collected from participants (see Figure 1).

Initial analyses from SUCCEED demonstrated a need to incorporate all the data available on a woman's histology, cytology, and HPV state to classify disease accurately. The standard method of classifying disease progression by histology alone (i.e., cervical intraepithelial neoplasia [CIN]1, to CIN2, then to CIN3, and finally cancer) is now yielding to a more molecular-based approach. Analyses from SUCCEED demonstrate a delineation of histologic stages by HPV infection. In an analysis that integrated molecular, histologic, cytologic, and epidemiologic data, SUCCEED data suggested that, while CIN2 unrelated to HPV-16 may reflect a combination of CIN1 and CIN3, HPV-16–related CIN2 may represent a precancerous state (Wang et al., *Cancer Epidemiol Biomarkers Prev* 2009; 18(1):113–120). In another analysis, hierarchical clustering of histology-cytology groups based on distributions of HPV genotype distinguished five increasingly severe diagnostic groups (see Figure 2). SUCCEED investigators

Although HPV infection may lead to the development of cervical cancer, the majority of women with HPV infections will not develop cancer, and many may never even develop cervical abnormalities.

hypothesize that the addition of molecular events to the histologic-cytologic analysis will further refine the categories and understanding of progressive disease.

Efforts are also under way to identify potential risk biomarkers by creating microarray gene expression profiles from lesional and normal cells. Initial analyses in collaboration with the University of Wisconsin at Madison demonstrated differences in patterns of gene expression by histologic grade. Further refinement of disease progression beyond the conventional histologic schema is ongoing, with a focus on differentiating molecular events between precancer and cancer. Also planned is an evaluation of complementary biologic events (e.g., microRNA, methylation, and HPV integration). Longer-term plans include assessment of gene expression by lower-grade lesions and by HPV genotype. ■

—Sophia S. Wang, Ph.D.

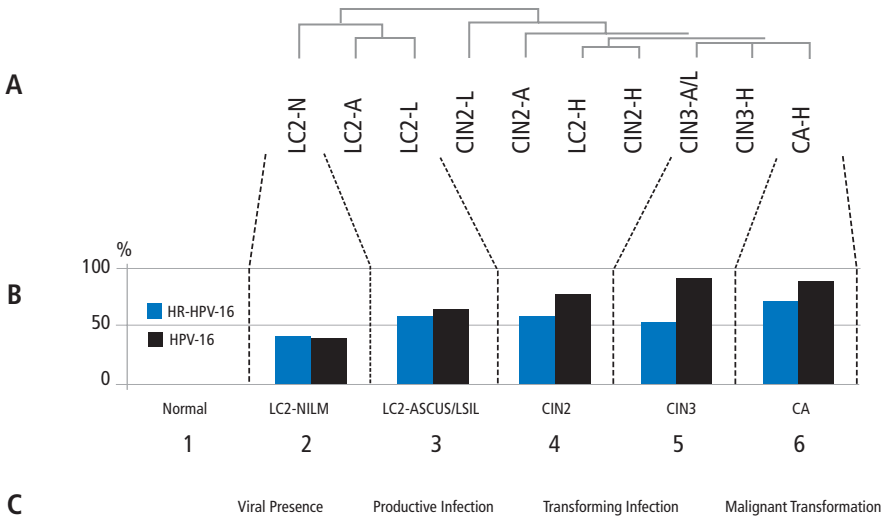


Figure 2. Disease stages identified in the SUCCEED population based on histology, cytology, and HPV genotyping. *(A)* Dendrogram of histology-cytology combination clustered by HPV genotype frequencies. *(B)* Viral load by disease stage: (1) women with normal histology, normal cytology, and HPV negativity; (2) HPV-positive women with < CIN2-NILM and low-level viral activity; (3) HPV-positive women with productive viral infections; (4) CIN2; (5) CIN3; and (6) cancer. *(C)* Functional viral-host interaction during cervical carcinogenesis correlating to the findings in the SUCCEED population. [A: atypical squamous cells of undetermined significance (ASCUS); H: high-grade squamous intraepithelial lesion (HSIL); L: low-grade squamous intraepithelial lesion (LSIL); LC2: < CIN2; N: negative for intraepithelial lesion or malignancy (NILM).] HPV types are grouped by species. (Wentzensen N, et al. 2009)

BENCH-TO-BEDSIDE AWARD TARGETS LI-FRAUMENI SYNDROME

Congratulations to Dr. Phillip Dennis from NCI's Center for Cancer Research, Dr. David Malkin from the University of Toronto, **Sharon A. Savage, M.D.,** Clinical Genetics Branch, and **Joseph F. Fraumeni, Jr., M.D.,** Division Director, who received an NIH Bench-to-Bedside Award for their project "Repositioning metformin as an anti-cancer agent in Li-Fraumeni syndrome."

Dr. Dennis is leading this multidisciplinary project and will be working with Drs. Malkin, Savage, and Fraumeni to assess the safety and efficacy of metformin as a treatment option for patients with Li-Fraumeni syndrome (LFS), a rare, inherited disorder that predisposes young people to certain cancers, including breast cancer, sarcomas, and a variety of other tumors. LFS is characterized by germline mutations in the *p53* tumor suppressor gene, which occur in approximately 70 percent of patients diagnosed with LFS. Previous studies suggest that metformin, which is currently used as an antidiabetic agent, may hold promise as an anticancer agent due to its ability to stimulate the AMP-activated protein kinase pathway, which plays a role in cellular metabolism and regulation. Metformin has also been shown in xenografts to inhibit the growth of *p53*-deficient tumors. The current study will determine whether metformin can prevent tumor formation or cause tumor regression in animal models of LFS, and it will also investigate the efficacy and safety of metformin through a clinical trial with LFS patients. Currently, few medical options exist for the treatment or prevention of LFS.

The NIH Bench-to-Bedside Award Program fosters collaborations among laboratory, clinical, and population scientists in areas of research that have potential for improving the understanding of an important disease process or for leading investigators to a new therapeutic, preventive, or diagnostic intervention. Projects involving extramural partners are encouraged. The awards are funded with contributions from the Office of Rare Diseases Research, Office of AIDS Research, Office of Research on Women's Health, the National Center on Minority Health and Health Disparities, the National Center for Research Resources, and matching Institute funds.

SCIENCE WRITERS' SEMINAR ON GENOME-WIDE ASSOCIATION STUDIES

In March, DCEG scientists helped science writers understand the complexity of genome-wide association studies (GWAS) by holding an NCI-sponsored Science Writers' Seminar titled "Genome-wide association studies in cancer research." The seminar was designed to educate journalists on the fundamental concepts of GWAS. "This promising technology enables researchers to identify novel regions of the genome associated with susceptibility to cancer," commented **Margaret A. Tucker, M.D.,** Director of the Human Genetics Program and Chief of the Genetic Epidemiology Branch (GEB). "The analysis and interpretation of these studies are quite complex, making the results difficult for reporters or the general audience to evaluate. Our researchers and the audience appreciated the interactive nature of the seminar and the opportunity to better communicate the science." Approximately 40 people attended, including representatives from *Science, JNCI, Nature,* and *Newsweek.*

Seminar speakers: (front) Laufey Amundadottir and Patricia Hartge; (back) Neil Caporaso, Margaret Tucker, Sholom Wacholder, and Stephen Chanock. *(Photo Credit: Hannah Arem)*

Stephen J. Chanock, M.D., Director of the Core Genotyping Facility (CGF) and Chief of the Laboratory of Translational Genomics (LTG), opened the seminar with a discussion of the history, success, and promise of GWAS. Dr. Chanock explained how the testing of millions of single nucleotide polymorphisms (SNPs) across the genome can uncover regions of a chromosome associated with greater disease risk. "By studying large populations of individuals with and without disease, GWAS can provide powerful indicators as to which SNP variations are associated with various cancers," Dr. Chanock said. "An in-depth understanding of the biology underlying the contribution of these genetic variations may one day lead to new approaches for therapy or prevention of specific cancers."

Laufey Amundadottir, Ph.D., an investigator in LTG, discussed downstream analyses, such as fine mapping, to identify the specific loci associated with risk and to determine the biological function of these loci. **Sholom Wacholder, Ph.D.,** a senior investigator in the Biostatistics Branch, provided a tutorial on statistical challenges and cautioned the reporters to carefully evaluate GWAS findings. He also spoke about goals for better predicting individual disease risk by incorporating SNPs into risk assessment models. **Patricia Hartge, Sc.D.,** Deputy Director of the Epidemiology and Biostatistics Program, explained the importance of well-defined study groups, focusing on the value of NCI's Cohort Consortium and other initiatives in providing the epidemiologic data that may elucidate gene-environment interactions. By using GWAS of pancreas, breast, and prostate cancers as examples, Dr. Hartge discussed the epidemiological considerations in designing GWAS and the extensive partnerships between intramural and extramural researchers. **Neil Caporaso, M.D.,** a senior investigator in GEB, presented his recently published findings on smoking behavior, adding a practical example to the seminar's overall theme. Dr. Caporaso's study focused on the biology of smoking behavior, revealing associations with the dopamine pathway and the nicotinic receptor.

The seminar concluded with a tour of the Advanced Technology Center to see the high-tech approaches employed in GWAS. CGF staff, including **Amy Hutchinson, M.S.,** Director of Operations, **Laurie Burdett, Ph.D.,** Lead Project Manager, and **Belynda Hicks, M.S.,** Quality Control Manager, gave a real-time presentation of the technologies and steps used to perform GWAS. ■

—Hannah Arem, M.H.S.

DCEG ASSEMBLES TWO NEW REVIEW COMMITTEES

DCEG has developed two new groups to review proposals and prioritize new projects that use NCI's Core Genotyping Facility (CGF) and Hormone Measurement Laboratory at NCI-Frederick.

The Genotyping Review Committee, chaired by **Margaret A. Tucker, M.D.,** Director of the Human Genetics Program and Chief of the Genetic Epidemiology Branch (GEB), conducts rigorous scientific review and prioritizes proposals for projects involving genotyping at CGF. Proposals are judged by their potential impact on biological concepts, clinical practice, and public health; epidemiologic rigor, including statistical power and analytic approaches; innovation and relevance of selected genes/pathways/approaches; and feasibility. Members serve one-year terms. Currently serving are **Demetrius Albanes, M.D.,** Nutritional Epidemiology Branch; **Neil E. Caporaso, M.D.** (GEB); **Stephen J. Chanock, M.D.,** Director of CGF and Chief of the Laboratory of Translational Genomics; **Michael B. Cook, Ph.D.,** Hormonal and Reproductive Epidemiology Branch (HREB); **Phuong Mai, M.D.,** Clinical Genetics Branch; **Lindsay M. Morton, Ph.D.,** Radiation Epidemiology Branch; **Ruth M. Pfeiffer, Ph.D.,** Biostatistics Branch; **Karen E. Pitt, Ph.D.,** Office of the Director; **Nathaniel Rothman, M.D., M.P.H., M.H.S.,** Occupational and Environmental Epidemiology Branch; and **Kelly Yu, M.P.H.,** Infections and Immunoepidemiology Branch.

"Because of the increasing demand on CGF as a resource to conduct high-throughput genotyping for molecular epidemiology studies and, most recently, large-scale genome-wide association and candidate gene studies, it became necessary to add a specialized task force to vet the science," Dr. Tucker said. "This process has increased the level of transparency and efficiency in completing genotyping and genomic projects within the Division."

The Genotyping Review Committee conducts rigorous scientific review and prioritizes proposals for projects involving genotyping at CGF. The Hormone Laboratory Advisory Committee is responsible for reviewing and prioritizing projects using the Hormone Measurement Laboratory within the Laboratory of Proteomics and Analytical Technologies at NCI-Frederick.

After project proposals have been reviewed by the committee, the lead investigator receives reviewer scores, comments, and the status of the proposal. Approved proposals are placed in a queue, at which time biorepositories are informed that the project's samples may be prepared for shipment to CGF.

The Hormone Laboratory Advisory Committee (HLAC), chaired by **Louise A. Brinton, Ph.D.,** Chief of HREB, is composed of scientific and administrative representatives from DCEG, the Center for Cancer Research (CCR), and SAIC-Frederick and is responsible for reviewing and prioritizing projects using the Hormone Measurement Laboratory within the Laboratory of Proteomics and Analytical Technologies (LPAT) at NCI-Frederick. This laboratory provides a new resource that can reliably measure levels of estrogen and 15 estrogen metabolites in urine and serum using sequential liquid chromatography-mass spectroscopy methods, and it will expand to involve additional analytes and media. "The anticipated demand on this facility is great," Dr. Brinton explained. "NCI needed to mobilize a strong cadre of staff to effectively manage the influx of projects through sound scientific and administrative review and prioritization." The committee acts in an advisory capacity and, after initial review and scoring, makes recommendations to the directors of DCEG and CCR for final determination.

The HLAC members, who serve two-year terms, include **Marianne K. Henderson, M.S.,** Chief, Office of Division Operations and Analysis; Dr. Walter Hubert, Office of Scientific Operations, NCI-Frederick; Dr. Larry Keefer, Chief, Laboratory of Comparative Carcinogenesis, CCR; Dr. Pfeiffer; Dr. Nancy Potischman, Applied Research Program, Division of Cancer Control and Population Sciences; Dr. Tim Veenstra, Director, LPAT, SAIC-Frederick; **Alyssa Voss, M.P.H.,** Office of Communications and Special Initiatives; Dr. Samuel Wells, Surgery Branch, CCR; Dr. Xia Xu, LPAT, SAIC-Frederick; and **Regina G. Ziegler, Ph.D., M.P.H.,** Epidemiology and Biostatistics Program. ■

—Alyssa Voss, M.P.H.

FIRST ANNUAL FELLOWS' TRAINING SYMPOSIUM

February marked the First Annual DCEG Fellows' Training Symposium, titled "Building scientific and social networks." The event was sponsored by the Office of Education and organized by a group of DCEG fellows, including committee cochairs **Melissa Rotunno, Ph.D.,** Genetic Epidemiology Branch (GEB), and **Sara Schonfeld, M.P.H.,** Radiation Epidemiology Branch; and **Michael B. Cook, Ph.D.,** Hormonal and Reproductive Epidemiology Branch (HREB); **Linda Dong, Ph.D.,** Occupational and Environmental Epidemiology Branch; **Jill Koshiol, Ph.D.,** Infections and Immunoepidemiology Branch; **Tram Kim Lam, Ph.D.** (GEB); **Rayna Matsuno Weise, M.P.H.,** Biostatistics Branch; **Joanne L. Watters, Ph.D., M.P.H.,** Nutritional Epidemiology Branch; and **Hannah P. Yang, Ph.D., Sc.M.** (HREB). The aims of the symposium were to bring fellows together to expand their networks, establish new collaborations, and gain valuable insight from DCEG leaders and former fellows. More than 60 pre-and postdoctoral fellows, representing all the DCEG branches and laboratories, participated in the event.

Fellows' Symposium organizing committee: (front) Hannah Yang, Kristin Kiser, Jackie Lavigne, Linda Dong, Sara Schonfeld, and Tram Lam; (back) Michael Cook, Jill Koshiol, Melissa Rotunno, Joanne Watters, and Tess Lee. (Not shown: Rayna Matsuno Weise.) *(Photo Credit: Bill Branson)*

Joseph F. Fraumeni, Jr., M.D., Division Director, began the symposium with "DCEG: An evolutionary history in the year of Darwin." Dr. Fraumeni spoke on the history of the Division, reviewing the innovative ideas and challenging decisions that have shaped DCEG and advanced scientific research. In "Networks, safety nets, and balance beams," **Shelia Hoar Zahm, Sc.D.,** DCEG Deputy Director, talked about her career path to and within DCEG, addressing such topics as maintaining a balance between work and life and how to select projects and mentors. Two former DCEG fellows—Dr. Ulrike Peters, Assistant Professor, Fred Hutchinson Cancer Research Center, and Dr. Anand Chokkalingam, Adjunct Assistant Professor, University of California, Berkeley—spoke about their experiences in transitioning from fellows to extramural investigators. Dr. Peters, in "Transition from a postdoc to an independent investigator: How to prepare for grant writing," talked about how she learned to select the best grant mechanisms and balance the writing of grants with other academic and research commitments. Dr. Chokkalingam, in "A (limited) tour of epidemiology outside of DCEG," drew on his experiences to compare and contrast working in industry with working in academia. The morning concluded with a lively panel discussion in which the speakers answered questions from participants.

The afternoon consisted of a poster session that featured the work of nearly 30 fellows. The session provided the attendees with an opportunity to learn about fellows' research projects and to talk about scientific findings.

Former fellows Anand Chokkalingam and Ulrike Peters answer questions from participants. *(Photo Credit: Bill Branson)*

The day concluded with oral presentations by three postdoctoral fellows, **Shahinaz Gadalla, M.D., Ph.D.,** Clinical Genetics Branch (CGB), on "Cancer risk in patients with myotonic dystrophy: A population-based study"; **Gretchen L. Gierach, Ph.D., M.P.H.** (HREB), on "Mammographic density does not differ between unaffected *BRCA1/2* mutation carriers and women at low-to-average risk of breast cancer"; and **Lisa Mirabello, Ph.D.** (CGB), on "Ovarian cancer risk is associated with leukocyte telomere length in the population-based Polish Ovarian Cancer Study." ■

—Melissa Rotunno, Ph.D., and Sara Schonfeld, M.P.H.

DCEG PARTICIPATES IN THE 100TH ANNUAL AACR MEETING

In April, many DCEG members attended the 100th Annual Meeting of the American Association for Cancer Research (AACR) in Denver. This event brought together researchers from around the world to highlight the most prominent advances in understanding cancer etiology, treatment, and prevention. **Joseph F. Fraumeni, Jr., M.D.,** Division Director, received the AACR Award for Lifetime Achievement in Cancer Research (see back cover).

More than 30 posters involving DCEG researchers were chosen for presentation. Several posters were highly rated, a designation for an abstract scoring in the top 3 to 4 percent of posters presented; a few also received awards or recognition by the press. Occupational and Environmental Epidemiology Branch (OEEB) investigators **Linda Dong, Ph.D.,** and **Min Shen, M.D., Ph.D.,** won AACR-Aflac Scholar-in-Training Awards for their highly rated posters "Urinary prostaglandin E2 metabolite and gastric cancer risk in the Shanghai Women's Health Study" and "A prospective study of telomere length and risk of lung cancer," respectively. Other researchers with highly rated posters included **H. Dean Hosgood, III, Ph.D.** (OEEB), "Mitochondrial DNA copy number and lung cancer risk in a prospective cohort study"; **Maria Teresa Landi, M.D., Ph.D.,** Genetic Epidemiology Branch (GEB), "MicroRNA expression, tobacco smoking, and genetic polymorphisms in lung cancer histology and survival"; **Lee E. Moore, Ph.D.** (OEEB), "VHL gene alteration and histopathologic risk factors in a large renal cancer case-control study"; **Mark Purdue, Ph.D.** (OEEB), "A prospective study of serum soluble CD30 concentration and risk of non-Hodgkin lymphoma"; and **Huei-Ting Tsai, Ph.D.** (GEB), "Evidence of immune disruption up to 9.8 years prior to diagnosis of chronic lymphocytic leukemia: A prospective study," which was presented at a press conference by **Neil E. Caporaso, M.D.** (GEB).

Stephen J. Chanock, M.D., Director of the Core Genotyping Facility and Chief of the Laboratory of Translational Genomics (LTG), cochaired the symposium "Genome-wide association studies (GWAS) in cancer: Current and future directions" and presented "Discovery of new loci in GWAS of common cancers." **Montserrat García-Closas, M.D., Dr.P.H.,** Hormonal and Reproductive Epidemiology Branch (HREB), chaired and introduced the symposium "Development and characterization of biomarkers for epidemiological studies."

Other DCEG presenters included **Laufey Amundadottir, Ph.D.** (LTG), "Genetic risk factors for pancreatic cancer from genome-wide association studies"; **Eric A. Engels, M.D., M.P.H.,** Infections and Immunoepidemiology Branch, "Viruses, immunity, and cancer"; **Ann W. Hsing, Ph.D.** (HREB), "High prevalence of screen-detected prostate cancer in West Africans: Implications for racial disparity of prostate cancer"; **Mitchell H. Gail, M.D., Ph.D.,** Biostatistics Branch, "The value for clinical and public health decisions of adding single nucleotide polymorphisms to a model to project breast cancer risk"; and **Nathaniel Rothman, M.D., M.P.H., M.H.S.** (OEEB), "Principles of biomarker characterization for epidemiological studies" and "Environmental and occupational cancer research in the age of genomics." ■


Gloria Gridley

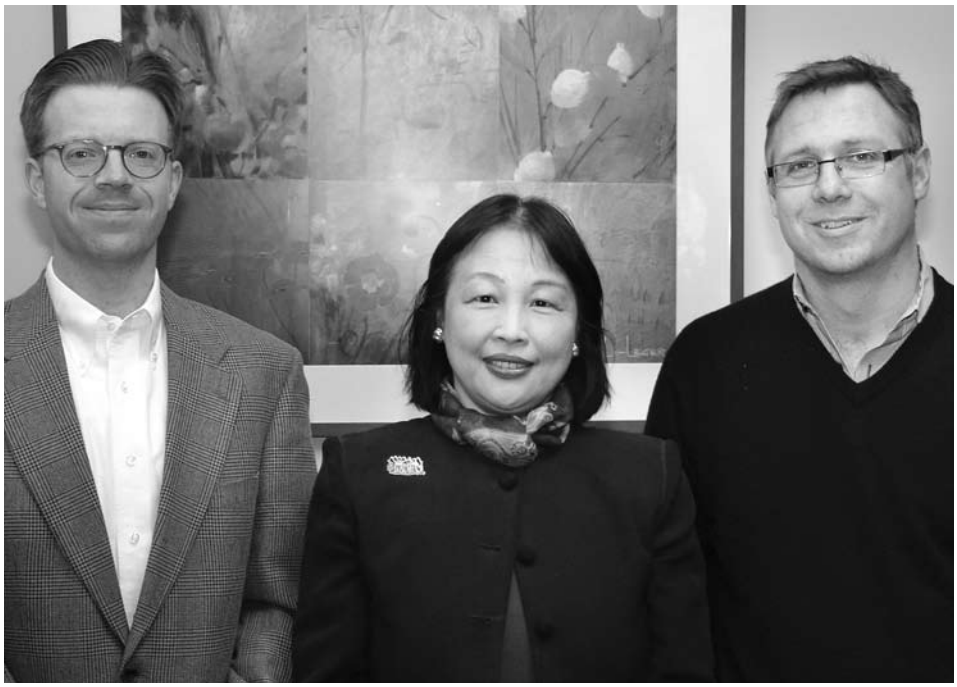
GLORIA GRIDLEY RETIRES

In April, **Gloria Gridley, M.S.,** Biostatistics Branch, retired after 28 years at NCI. She received a B.S. in microbiology from the University of Maryland and an M.S. in biostatistics/epidemiology from Georgetown University. Before coming to NCI, she worked in private industry and at a variety of government agencies, including the U.S. Department of Agriculture, the U.S. Department of Health and Human Services, and the Uniformed Services University of the Health Sciences. She joined NCI's Environmental Epidemiology Branch, now called the Hormonal and Reproductive Epidemiology Branch, as a statistician in 1981 and transferred to the Biostatistics Branch in 1995. Her research has covered a wide range of cancers and a variety of risk factors for cancer, particularly occupation, nutrition, and medical conditions. She has studied both adult cancers and perinatal risk factors for childhood cancers as well as cancer risk when exposures occurred in childhood. She has developed large administrative databases—containing dietary, census, and medical data—into epidemiologic resources and has worked on several large and long-term international studies in Scandinavia and Shanghai as well as on a large study of U.S. veterans. She has been a generous mentor, teaching and helping DCEG staff and investigators from around the world to use these valuable resources for their research.

Ms. Gridley serves on the Rockville Science and Technology Commission; volunteers for the Washington Statistical Society in the Quantitative Literacy Program and in the Adventures in Science program at NIH; and has been a science fair judge in Maryland, Virginia, and Washington, DC. She is active in Graduate Women in Science and recently, as a co-historian, edited an 87-year history of the organization, which will be published in 2009. Ms. Gridley also loves to contra-dance and square-dance, traveling all over the country in pursuit of this hobby.

TRANSITIONS IN THE PLCO STUDY

One of DCEG's central missions is to develop infrastructure, resources, and strategic partnerships in molecular epidemiology across NCI, NIH, and the extramural community. Few studies embody this mission better than the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. This population-based randomized trial, which evaluates screening programs for prostate, lung, colorectal, and ovarian cancers, enrolled more than 150,000 healthy men and women, ages 55 to 74, at 10 screening centers nationwide between 1993 and 2001. Its design and data, results and research, and broadly based biospecimens make the PLCO study a premier resource for cutting-edge epidemiologic research for a wide variety of cancers. From the beginning, NCI's Division of Cancer Prevention (DCP) and DCEG have effectively collaborated on the design, implementation, and oversight of all aspects of the study.



James Lacey, Ann Hsing, and Mark Purdue.

During the next few years, the majority of the participants will have completed their scheduled six years of screening and seven years of follow-up and will no longer be actively followed by DCP. The efforts of the screening centers that enrolled, screened, and followed the participants and the exceptional

FUTURE DIRECTIONS FOR THE PLCO STUDY

Biorepository: The PLCO study includes a wide variety of stored biospecimens (i.e., serum, plasma, buffy coat, red blood cells, whole blood, and buccal cells) for use in research projects conducted under PLCO Etiologic and Early Markers initiatives. The availability of serial blood-based specimens makes PLCO ideally suited for investigations of early-disease markers. **Mark Purdue, Ph.D.,** Occupational and Environmental Epidemiology Branch, will lead efforts to oversee and optimize the use of these biospecimens.

Tissue: Tumor tissue has been collected from PLCO participants who developed prostate, lung, colorectal, or ovarian cancer during the study. Future collections will focus on other tumors to expand the existing tissue microarrays and tissue cores that can be combined with other biospecimens, questionnaires, and screening examinations for insights into the entire spectrum of carcinogenesis. **James V. Lacey, Jr., Ph.D.,** Hormonal and Reproductive Epidemiology Branch (HREB), will guide the expansion and exploration of these tissue resources.

Strategic Planning: Transformation of the PLCO trial into a long-term follow-up study will greatly enhance the value of PLCO in future molecular and genetic epidemiologic research. DCEG and DCP are collaboratively creating plans to continue participant follow-up, collect additional information on exposures and endpoints, and preserve open and fair access for intramural and extramural investigators. **Ann W. Hsing, Ph.D.** (HREB), will lead the strategic planning process to maintain the PLCO study as an excellent resource for the next generation of cutting-edge research.

overall navigation by DCP, especially by Dr. Christine Berg, the project officer, have been integral in establishing the extensive data and biospecimens available in the PLCO study. For DCEG, the conclusion of the screening component of the study presents an opportunity to shape the collaborative long-term follow-up of participants. The conversion of the PLCO trial into a long-term cohort study, a strategy that has been successful in previous NCI studies, underscores the enormous value of this resource in the molecular epidemiology of cancer.

Ann W. Hsing, Ph.D., Hormonal and Reproductive Epidemiology Branch (HREB), **James V. Lacey, Jr., Ph.D.** (HREB), and **Mark Purdue, Ph.D.,** Occupational and Environmental Epidemiology Branch (OEEB), have accepted the responsibility of leading the DCEG effort in the PLCO study after the retirement of **Richard B. Hayes, D.D.S., Ph.D.** (OEEB), the leader of DCEG's PLCO efforts since the trial's inception. Drs. Hsing, Lacey, and Purdue have been collaborating with DCP and the numerous stakeholders, both intramural and extramural, on the future direction of PLCO. They will be working to organize DCEG's collaborative role in long-term follow-up, refine policies and procedures, and ensure that all systems are in place for intramural and extramural scientists to use the resources of the PLCO study. ■

—James V. Lacey, Jr., Ph.D.,
Ann W. Hsing, Ph.D., and
Mark Purdue, Ph.D.

PEDIATRIC RADIATION RISKS

Researchers in DCEG's Radiation Epidemiology Branch (REB) have updated their popular professional education brochure *Radiation Risk and Pediatric Computed Tomography: A Guide for Health Care Providers.* Originally created in 2002 in response to the dramatically increased use of diagnostic and interventional radiologic procedures, **Ruth A. Kleinerman, M.P.H.,** and **Elaine Ron, Ph.D., M.P.H.,** collaborated with the Society for Pediatric Radiology to increase awareness of the need to minimize the levels of radiation to which children are exposed through these procedures. "A key element of the brochure is the table showing the differences in radiologic dose between child and adult settings," Ms. Kleinerman said. Because computed tomography (CT) scans are often conducted at adult settings and doses, children have been exposed to radiation levels much higher than necessary. Several decades of epidemiologic research have shown that children are considerably more sensitive to late radiation effects than adults and, because of their young age, have many more years to develop radiation-related cancers than do adults. The risk for developing a radiation-related cancer can be several times higher for a young child than for an adult exposed to an identical CT scan.

Dr. Ron and Ms. Kleinerman have updated the brochure to reflect the improvements made in pediatric radiologic practices since its initial release in 2002. Dr. Kwang Pyo Kim, former dosimetrist for REB, revised the exposure table using data derived from recent literature, showing doses in ranges rather than as single numbers. The revised table shows a reassuring decrease in doses to the head among children.

"Since its initial release, there has been a tangible reaction in the medical radiology community to this information and adoption of the 'as low as reasonably achievable' concept," said Dr. Ron, who continues to study the effects of childhood exposure to radiation in various populations. "We hope this new information continues to increase awareness, not only in pediatric radiologists, but also family practice doctors and pediatricians, and results in a measurable decline in the overall doses to which children are exposed through these procedures."

The brochure is available online at http://www.cancer.gov/cancertopics/causes/radiation-risks-pediatric-CT.

—Alyssa Voss, M.P.H.

CT exam type	Setting	Relevant organ	Absorbed organ dose range estimate (mGy)
Head	Adult[1]	Brain	23–49
	Child[2]	Brain	11–25
Abdomen	Adult[1]	Stomach	21–43
	Child[2]	Stomach	5–11

Absorbed organ doses in children by exam type: (1) using an adult setting and (2) using a setting modified for children.

WORKSHOP ON MERKEL CELL CARCINOMA

In January, DCEG, the NCI Office of HIV and AIDS Malignancy (OHAM), and the NIH Office of Rare Diseases Research cosponsored a workshop titled "Merkel cell carcinoma: Basic, epidemiologic, translational and clinical research." The workshop was motivated by the recent discovery that Merkel cell carcinoma (MCC) is associated with a previously unknown human polyomavirus, provisionally designated MCPyV. **James J. Goedert, M.D.,** a senior investigator in the Infections and Immunoepidemiology Branch (IIB), and **Kishor Bhatia, M.D.,** Director of OHAM's AIDS Malignancy Program and adjunct investigator in IIB, introduced the workshop topic and welcomed the participants, which included dermatologists, virologists, surgeons, epidemiologists, pathologists, and patient representatives.

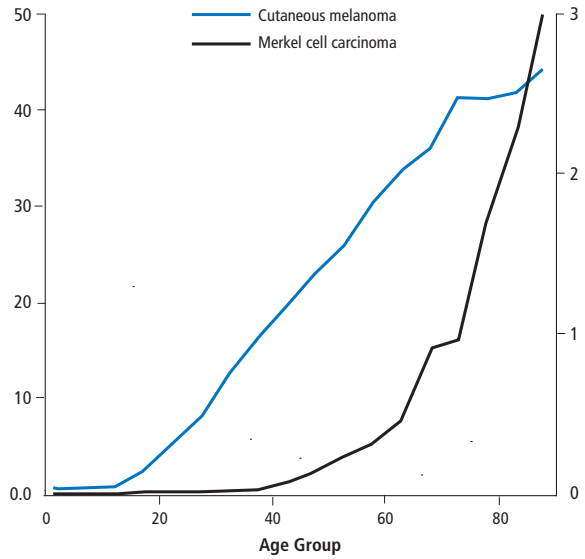


Figure 1. Incidence of cutaneous melanoma and Merkel cell carcinoma of skin by age based on Surveillance, Epidemiology and End Results program data, 1986–1994. (Miller RW, and Rabkin CS, 1999)

MCC is a rare, aggressive malignancy of cutaneous neuroectodermal cells. **Eric A. Engels, M.D., M.P.H.,** a senior investigator in IIB, presented an overview of the epidemiology of this disease. He noted that MCC has an annual incidence of 3 per million in the United States, has a two-year mortality rate of 28 percent, and is extremely rare before age 50 but becomes much more common thereafter (see Figure 1). **Charles S. Rabkin, M.D.,** a senior investigator in IIB, discussed work with the late Dr. Robert Miller, a founder of NCI's epidemiology program, and observed that the incidence of MCC was significantly associated with European ancestry; exposure to ultraviolet (UV) radiation; and several second malignancies, including melanoma and non-melanoma skin cancers, multiple myeloma, non-Hodgkin lymphoma, and chronic lymphocytic leukemia. More recently, Dr. Engels and other IIB investigators have shown that the risk of MCC is increased 11-fold among people with AIDS and 5-fold among people with an organ transplant.

Additional presentations centered on the discovery of MCPyV, the epidemiology and virology of other polyomaviruses, the microscopic and immunopathological features of normal Merkel cells and MCC, and the assessment and clinical management of patients with MCC. Preliminary reports suggest that MCPyV, like other polyomaviruses, is acquired in childhood and is widespread among adults.

Two breakout groups identified gaps in knowledge and priorities for research. The virology and epidemiology group highlighted the urgent need for tools to detect, quantify, and elucidate the epidemiology and natural history of MCPyV. Such tools would be used to understand the relationships of viral regulation, immune deficiency, UV exposure, and host factors to MCC risk, and they could be applied to determine whether hematopoietic or other malignancies are related to MCPyV infection. The molecular pathology and clinical management group strongly advocated the development of consortia to evaluate whether sentinel lymph node biopsy, adjuvant radiation therapy, or antiviral or other investigational therapies are effective in reducing mortality from MCC. The workshop participants endorsed expanded use of online communications via the MCC clinical referral and treatment group (www.merkelcell.org) and the patient discussion group (http://groups.google.com/group/merkelcell).

The proceedings of the workshop have been submitted for publication, and IIB investigators are developing collaborations to further understand this malignancy. ■

—James J. Goedert, M.D.

RICHARD HAYES RETIRES

In January, **Richard B. Hayes, D.D.S., Ph.D.,** retired from the Occupational and Environmental Epidemiology Branch after a 23-year career at NCI. "Dr. Hayes advanced research on occupational risk factors for cancer and forged new ground by incorporating molecular technology into epidemiologic research," said **Joseph F. Fraumeni, Jr., M.D.,** Division Director.

Richard Hayes, Debra Silverman, and Joseph Fraumeni.

Dr. Hayes was born and raised on Long Island, New York. After earning a B.S. in biology from Manhattan College and a D.D.S. from Columbia University, he worked in dentistry before pursuing interests in public health. He earned an M.P.H. and Ph.D. in epidemiology from Johns Hopkins University, where his doctoral dissertation reported an increased risk of lung cancer mortality among workers at a chromium chemical production plant, resulting in the closure of the facility. Before joining NCI in 1985, he worked as an epidemiologist at the Dutch Cancer Foundation and the Medical School at Erasmus University in Rotterdam.

"Dr. Hayes advanced research on occupational risk factors for cancer and forged new ground by incorporating molecular technology into epidemiologic research."

While at NCI, Dr. Hayes published more than 250 peer-reviewed manuscripts and fostered a collegial work environment, collaborating with scientists all over the world and mentoring numerous young scientists. He was responsible for substantially increasing our understanding of the cancer hazards of benzene, formaldehyde, and other occupational exposures, including finding a dose-related association between benzene exposure and hematologic malignancies. In 1992, he began incorporating etiologic and early-marker studies into the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, transforming PLCO into an invaluable resource for cohort studies in molecular epidemiology. His scientific contributions have been instrumental in elucidating the role of genetic, nutritional, and behavioral risk factors for tumors of the prostate and large bowel, including cancers and adenomas. He also has been on the forefront of genetic research for prostate cancer as part of the Breast and Prostate Cancer Cohort Consortium and Cancer Genetic Markers of Susceptibility project, providing insight into the reported association between *KLK3* and other genetic variants and risk of prostate cancer. His achievements have been recognized with an array of awards, including the Alice Hamilton Science Award for Occupational Safety and Health, NCI and NIH Merit Awards, and the NCI Mentor of Merit Award.

Dr. Hayes leaves NCI to become the Director of the Division of Epidemiology, Department of Environmental Medicine, and Associate Director for Population Sciences at the New York University (NYU) Cancer Institute. He will continue investigating genetic and environmental risk factors for cancer, as well as their interactions, and will work to build a comprehensive cancer epidemiology and prevention research program at NYU. ■

—Sonja I. Berndt, Pharm.D., Ph.D.

DCEG HOLDS RETREAT FOR TENURE-TRACK INVESTIGATORS

DCEG held its fourth retreat for tenure-track investigators in February. Sponsored by the Committee of Scientists (COS), the half-day retreat provided information about the tenure process in the NIH intramural program and offered suggestions on how to accomplish research aims while on track for tenure. Approximately 20 tenure-track investigators participated in the event, which was organized by **Christian C. Abnet, Ph.D., M.P.H.,** Nutritional Epidemiology Branch; **Hormuzd A. Katki, Ph.D.,** Biostatistics Branch (BB); **Sam M. Mbulaiteye, M.D.,** Infections and Immunoepidemiology Branch (IIB); and COS chair **Katherine A. McGlynn, Ph.D., M.P.H.,** Hormonal and Reproductive Epidemiology Branch.

Participants in the tenure-track retreat with (front) Katherine McGlynn, Joseph Fraumeni, and Shelia Zahm.

Joseph F. Fraumeni, Jr., M.D., Division Director, opened the retreat with comments on "The road to tenure." Dr. Fraumeni described specific measures of progress that are important for achieving tenure at NIH. He emphasized the philosophy of research in DCEG and the unique characteristics of the Intramural Research Program that create a setting for high-impact, high-quality, distinctive science. Dr. Joan Schwartz, Assistant Director of the NIH Office of Intramural Research, spoke about the resources available at NIH to help tenure-track investigators. Dr. Barnett Kramer, Director of the Office of Medical Applications of Research and Associate Director of the NIH Office of Disease Prevention, presented his insights on how to craft a successful tenure package based on his experience with the NIH Central Tenure Committee as chair of the NIH Epidemiology and Biometry Review Panel. The presentations concluded with information on the tenure process from members of DCEG's Promotion and Tenure Review Panel, **Shelia Hoar Zahm, Sc.D.,** panel chair and Deputy Director of DCEG, and **Jay H. Lubin, Ph.D.** (BB). Dr. Zahm presented data on individuals who had been on tenure-track in DCEG, including distribution by gender, the average number of years before an investigator became tenured, and the quantity and authorship role of publications that individuals typically had when they were nominated for tenure. Dr. Lubin provided candid advice on how to have a successful tenure-track experience and important considerations for a tenure package.

The retreat ended with a panel discussion among recently tenured senior investigators **Eric A. Engels, M.D., M.P.H.** (IIB), **Ruth M. Pfeiffer, Ph.D.** (BB), and **Sophia S. Wang, Ph.D.** (IIB). Each spoke and answered questions about his or her experiences with becoming tenured. A lively discussion involving all retreat participants ensued.

The feedback concerning the event was highly positive, with most attendees indicating that they had learned a great deal about the tenure process. ■

—Katherine A. McGlynn, Ph.D., M.P.H.

NEW REPRESENTATIVES FOR STAFF SCIENTIST/STAFF CLINICIAN ORGANIZATION

DCEG SS/SC representatives: Dalsu Baris and Mark Roth.

Dalsu Baris, M.D., Ph.D., a staff scientist in the Occupational and Environmental Epidemiology Branch, has been elected to serve on the Council of Representatives for the NIH Staff Scientist/Staff Clinician (SS/SC) Organization. **Mark J. Roth, M.D.,** a staff clinician in the Nutritional Epidemiology Branch, has been appointed as the alternate DCEG representative.

Established in 2004, the NIH SS/SC Organization acts on behalf of the more than 1,000 staff scientists and clinicians who work in the NIH Institutes and Centers with intramural programs. The organization's objectives are to represent staff scientists and clinicians to the NIH administration, promote networking and interinstitute collaborations, create an information repository of the resources and expertise held by SSs/SCs, organize seminars and workshops on emerging technologies, and foster career development.

As the DCEG representatives, Drs. Baris and Roth will serve as the points of contact and liaisons for DCEG SSs/SCs, addressing their needs during the organization's meetings, and will help to establish initiatives that foster their career development.

SCIENTIFIC HIGHLIGHTS

ALL CANCERS

Dairy Food and Calcium Intake

Dairy food and calcium intake in relation to total cancer and cancer at individual sites was examined in the NIH-AARP Diet and Health Study. During an average of seven years of follow-up, 36,965 and 16,605 cancer cases in men and women, respectively, were identified. Calcium intake was not related to total cancer in men but was nonlinearly associated with total cancer in women; the risk decreased up to approximately 1,300 mg/d, above which no further risk reduction was observed (see Figure 1). In men and women, dairy food and calcium intakes were inversely associated with cancers of the digestive system, particularly for colorectal cancer. **(Park Y, Leitzmann MF, Subar AF, Hollenbeck A, Schatzkin A. Dairy food, calcium, and risk of cancer in the NIH-AARP Diet and Health Study. *Arch Intern Med* 2009;169:391–401)**

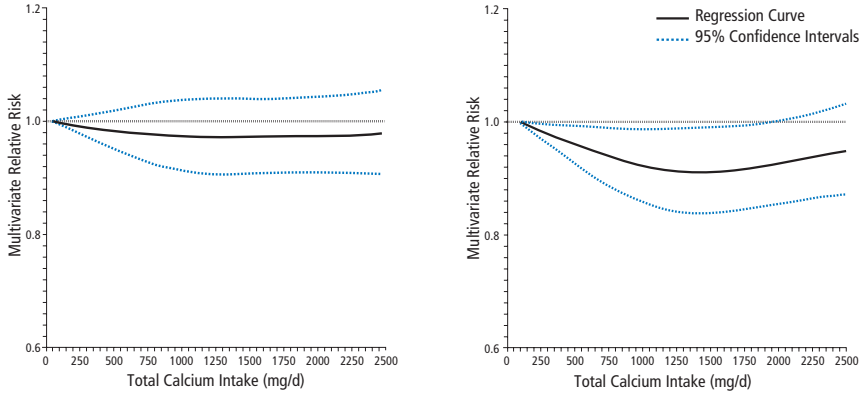


Figure 1. Nonparametric regression curve for the association between calcium intake and risk of all cancers for (A) men and (B) women. (Park Y, et al. 2009)

Occupational Exposure to Heterocyclic Aromatic Amine Pesticides

Cancer incidence was evaluated among 20,646 imazethapyr-exposed pesticide applicators enrolled in the Agricultural Health Study, a prospective cohort of 57,311 licensed pesticide applicators enrolled from 1993 to 1997. A total of 2,907 incident cancers developed through 2004. The authors found significant trends in risk with increasing lifetime exposure days for bladder cancer and colon cancer. Rate ratios increased by 137% for bladder cancer and 78% for colon cancer when those with highest exposure were compared to the nonexposed. The excess risk for colon cancer was limited to proximal cancers (rate ratio = 2.7). **(Koutros S, Lynch CF, Ma X, Lee WJ, Hoppin JA, Christensen CH, Andreotti G, Freeman LB, Rusiecki JA, Hou L, Sandler DP, Alavanja MC. Heterocyclic aromatic amine pesticide use and human cancer risk: Results from the U.S. Agricultural Health Study. *Int J Cancer* 2009;124:1206–1212)**

Risks by Type of Meat Intake

This study assessed the relationships of red, white, and processed meat intakes to risk for total and cause-specific mortality in the NIH-AARP Diet and Health Study. There were 47,976 male deaths and 23,276 female deaths during 10 years of follow-up. Men and women in the highest vs. lowest quintile of red (hazard ratio [HR] = 1.31 and 1.36, respectively) and processed meat (HR = 1.16 and 1.25, respectively) intakes had elevated risks for overall mortality. Men and women had elevated risks for cancer mortality for red (HR = 1.22 and 1.20, respectively) and processed meat (HR = 1.12 and 1.11, respectively) intakes and for cardiovascular disease mortality for red (HR = 1.27 and 1.50, respectively) and processed meat (HR = 1.09 and 1.38, respectively) intakes. When comparing the highest with the lowest quintile of white meat intake, there was an inverse association for total mortality and cancer mortality as well as for all other deaths for men and women. **(Sinha R, Cross AJ, Graubard BI, Leitzmann MF, Schatzkin A. Meat intake and mortality: A prospective study of over half a million people. *Arch Intern Med* 2009;169:562–571)**

BREAST CANCER

Two New Risk Alleles Identified

A three-stage genome-wide association study (GWAS) of breast cancer was conducted among 9,770 cases and 10,799 controls in the Cancer Genetic Markers of Susceptibility initiative. In stage one, 528,173 single nucleotide polymorphisms (SNPs) in 1,145 cases of invasive breast cancer and 1,142 controls were genotyped. In stage two, 24,909 top SNPs in 4,547 cases and 4,434 controls were analyzed. In stage three, the authors investigated 21 loci in 4,078 cases and 5,223 controls. Two new loci achieved genome-wide significance. A pericentromeric SNP on chromosome 1p11.2 (rs11249433) resides in a large linkage disequilibrium block neighboring *NOTCH2* and *FCGR1B;* this signal was stronger for estrogen receptor–positive tumors. A second SNP on chromosome 14q24.1 (rs999737) localizes to *RAD51L1,* a gene in the homologous recombination DNA repair pathway.

Associations with loci on chromosomes 2q35, 5p12, 5q11.2, 8q24, 10q26, and 16q12.1 were also confirmed. **(Thomas G, Jacobs KB, Kraft P, Yeager M, Wacholder S, Cox DG, Hankinson SE, Hutchinson A, Wang Z, Yu K, Chatterjee N, Garcia-Closas M, Gonzalez-Bosquet J, Prokunina-Olsson L, Orr N, Willett WC, Colditz GA, Ziegler RG, Berg CD, Buys SS, McCarty CA, Feigelson HS, Calle EE, Thun MJ, Diver R, Prentice R, Jackson R, Kooperberg C, Chlebowski R, Lissowska J, Peplonska B, Brinton LA, Sigurdson A, Doody M, Bhatti P, Alexander BH, Buring J, Lee IM, Vatten LJ, Hveem K, Kumle M, Hayes RB, Tucker M, Gerhard DS, Fraumeni JF Jr, Hoover RN, Chanock SJ, Hunter DJ. A multistage genome-wide association study in breast cancer identifies two new risk alleles at 1p11.2 and 14q24.1 *(RAD51L1). Nat Genet* 2009;41:579–584)**

CERVICAL CANCER

Human Papillomavirus Type and Precancerous Lesions

The authors investigated the timing of diagnosis of histologic cervical intraepithelial neoplasia grade 3 or worse (CIN3+) using data from the Atypical Squamous Cells of Undetermined Significance–Low-grade Squamous Intraepithelial Lesion Triage Study. Among women who were positive for human papillomavirus type 16 (HPV-16) at enrollment, 85% of CIN3+ were diagnosed at enrollment, compared with 57% and 58%, respectively, in women who were HPV-18/45 positive and other carcinogenic type–positive at enrollment. In contrast, among women who were HPV-16 positive at enrollment, only 7% of CIN3+ were diagnosed at study exit, compared with 31% and 21%, respectively, of CIN3+ diagnosed at study exit in women who were HPV-18/45 positive and other carcinogenic type–positive at enrollment. Results also indicate an underrepresentation of HPV-18/45 in precancers; whether this is due to occult pathology needs further investigation. **(Safaeian M, Schiffman M, Gage J, Solomon D, Wheeler CM, Castle PE. Detection of precancerous cervical lesions is differential by human papillomavirus type. *Cancer Res* 2009;69:3262–3266)**

ESOPHAGEAL AND GASTRIC CANCERS

Nutrient Supplementation

In a randomized cancer prevention trial conducted in Linxian, China, in which 29,584 adults were given daily vitamin and mineral supplements, treatment with "factor D"—a combination of 50 μg selenium, 30 mg vitamin E, and 15 mg beta-carotene—led to decreased mortality from all causes, cancer overall, and gastric cancer. Participants who received factor D had lower overall mortality (HR = 0.95; a reduction in cumulative mortality from 33.62% to 32.19%), and gastric cancer mortality (HR = 0.89; reduction in cumulative gastric cancer mortality from 4.28% to 3.84%) than subjects who did not receive factor D. Reductions were mostly attributable to benefits to subjects younger than 55 years. Factor D did not affect esophageal cancer mortality overall; however, this outcome decreased 17% among participants younger than 55 years (HR = 0.83) but increased 14% among those aged 55 years or older (HR = 1.14). Vitamin A and zinc supplementation was associated with increased total and stroke mortality; vitamin C and molybdenum supplementation was associated with decreased stroke mortality. **(Qiao YL, Dawsey SM, Kamangar F, Fan JH, Abnet CC, Sun XD, Johnson LL, Gail MH, Dong ZW, Yu B, Mark SD, Taylor PR. Total and cancer mortality after supplementation with vitamins and minerals: Follow-up of the Linxian General Population Nutrition Intervention Trial. *J Natl Cancer Inst* 2009;101:507–518)**

Nonsteroidal Anti-inflammatory Drug Use

The association between self-reported use of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) in the past 12 months and gastric noncardia (n = 182), gastric cardia (n = 178), and esophageal adenocarcinomas (n = 228) was examined in a prospective cohort (n = 311,115) followed for seven years. Use of aspirin (HR = 0.64) or other NSAIDs (HR = 0.68) was associated with a lower risk of gastric noncardia adenocarcinoma. No significant associations were found for either aspirin or other NSAIDs with gastric cardia cancer or esophageal adenocarcinoma. In a meta-analysis, aspirin or NSAID use was inversely associated with gastric and esophageal adenocarcinomas. **(Abnet CC, Freedman ND, Kamangar F, Leitzmann MF, Hollenbeck AR, Schatzkin A. Non-steroidal anti-inflammatory drugs and risk of gastric and oesophageal adenocarcinomas: Results from a cohort study and a meta-analysis. *Br J Cancer* 2009;100:551–557)**

Physical Activity

This study investigated the association between physical activity and esophageal and gastric carcinoma among 487,732 U.S. men and women in the NIH-AARP Diet and Health Study. Among 523 cases of esophageal carcinoma (149 squamous cell and 374 adenocarcinoma) and 642 cases of gastric carcinoma (313 cardia and 329 noncardia), physical activity was associated with reduced risk of combined esophageal and gastric adenocarcinomas but was unrelated to esophageal squamous cell carcinoma (ESCC). The inverse association with physical activity was strongest for gastric noncardia adenocarcinoma (relative risk [RR] for highest vs. lowest physical activity level = 0.62). Relationships were weaker and not significant for gastric cardia adenocarcinoma (RR = 0.83) and esophageal adenocarcinoma (RR = 0.75). No significant relationship with physical activity was observed for ESCC. **(Leitzmann MF, Koebnick C, Freedman ND, Park Y, Ballard-Barbash R, Hollenbeck A, Schatzkin A, Abnet CC. Physical activity and esophageal and gastric**

carcinoma in a large prospective study. *Am J Prev Med.* 2009;36:112–119)

Telomeres and Chromosome Instability

The association between genome-wide chromosomal changes in cancer cells and telomere length/attrition in cancer/stroma cells was investigated in 47 ESCC patients. Telomere length differed significantly among cell types, such that length in infiltrative lymphocytes was greater than length of carcinoma-associated fibroblasts (CAFs), which were longer than cancer cells. Shortened telomeres were observed in cancer cells in 94% of the tumors examined. Telomere length in CAFs was significantly associated with chromosomal instability on 4q and 13q, and lymphocyte telomere length was significantly associated with instability on chromosomal arm 15q. Telomere attrition in cancer cells, defined as the telomere length in CAFs minus the telomere length in cancer cells, was significantly associated with chromosomal instability on 13q and 15q. **(Zheng YL, Hu N, Sun Q, Wang C, Taylor PR. Telomere attrition in cancer cells and telomere length in tumor stroma cells predict chromosome instability in esophageal squamous cell carcinoma: A genome-wide analysis. *Cancer Res* 2009;69:1604–1614)**

GENETICS

Genome-wide and Candidate Gene Study of Smoking Behaviors

The contribution of genetic variation to smoking behaviors was investigated in a joint analysis of two GWAS in 2,329 men from the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial and 2,282 women from the Nurses' Health Study. Seven measures of smoking behavior, four continuous (cigarettes per day [CPD], age at initiation of smoking, duration of smoking, and pack years) and three binary (ever vs. never smoking, ≤ 10 vs. > 10 cigarettes per day [CPDBI], and current vs. former smoking) were analyzed. None of the SNPs achieved genome-wide significance ($p < 10^{-7}$) in any combined analysis pooling evidence across the two studies; between two and seven SNPs with $p < 10^{-5}$ for each of the seven measures were observed. In the chr15q25.1 region spanning the nicotinic receptors *CHRNA3* and *CHRNA5,* multiple SNPs associated with CPD ($p < 10^{-3}$) were identified, including rs1051730, which has been associated with nicotine dependence, smoking intensity, and lung cancer risk. The authors also selected 11,199 SNPs drawn from 359 *a priori* candidate genes and performed individual gene and gene-group analyses. Between two and five genes associated with each measure of smoking behavior were identified. Aside from *CHRNA3* and *CHRNA5, MAOA* was associated with CPDBI (gene-level $p < 5.4 \times 10^{-5}$). **(Caporaso N, Gu F, Chatterjee N, Sheng-Chih J, Yu K, Yeager M, Chen C, Jacobs K, Wheeler W, Landi MT, Ziegler RG, Hunter DJ, Chanock S, Hankinson S, Kraft P, Bergen AW. Genome-wide and candidate gene association study of cigarette smoking behaviors. *PLoS ONE* 2009;4:e4653)**

Mortality in Retinoblastoma Survivors

The authors examined cause-specific mortality among retinoblastoma survivors diagnosed between 1914 and 1996 at two U.S. institutions. A total of 151 deaths due to subsequent malignant neoplasms occurred among 1,092 hereditary retinoblastoma survivors (standardized mortality ratio [SMR] = 35) compared with 12 deaths among 762 nonhereditary retinoblastoma survivors (SMR = 2.5). Excess mortality from subsequent malignant neoplasms (particularly sarcomas, melanomas, and cancers of the brain and other parts of the nervous system) among hereditary retinoblastoma survivors extended beyond 40 years after retinoblastoma diagnosis. Elevated risk of death from lung cancer among hereditary retinoblastoma survivors was also confirmed. Relative rates of mortality from subsequent malignant neoplasms were higher among those who had been treated with radiotherapy than among those who had not. Cumulative mortality from subsequent malignant neoplasms at 50 years after retinoblastoma diagnosis was 25.5% for hereditary retinoblastoma survivors and 1.0% for nonhereditary retinoblastoma survivors (see Figure 2). **(Yu CL, Tucker MA, Abramson DH, Furukawa K, Seddon JM, Stovall M, Fraumeni JF Jr, Kleinerman RA. Cause-specific mortality in long-term survivors of retinoblastoma. *J Natl Cancer Inst* 2009; 101:581–591)**

HEAD AND NECK CANCERS

Risks Associated with Alcohol Type

The authors pooled data from 15 case-control studies of head and neck cancer (9,107 cases, 14,219 controls) to investigate associations with beverage consumption for subjects who drank beer only (858 cases, 986 controls), for liquor-only drinkers (499 cases, 527 controls), and for wine-only drinkers (1,021 cases, 2,460 controls) using never drinkers of alcohol (1,124 cases, 3,487 controls) as a common reference group. They observed similar associations with ethanol-standardized consumption frequency for beer-only drinkers (odds ratios [ORs] = 1.6, 1.9, 2.2, and 5.4 for ≤ 5, 6–15, 16–30, and > 30 drinks per week, respectively) and liquor-only drinkers (ORs = 1.6, 1.5, 2.3, and 3.6). Among wine-only drinkers, the ORs for moderate levels of consumption frequency approached the null, whereas the ORs for higher consumption levels were comparable to those of drinkers of other beverage types (ORs = 1.1, 1.2, 1.9, and 6.3). **(Purdue MP, Hashibe M, Berthiller J, La Vecchia C, Dal Maso L, Herrero R, Franceschi S, Castellsague X, Wei Q, Sturgis EM, Morgenstern H, Zhang ZF, Levi F, Talamini R, Smith E, Muscat J, Lazarus P, Schwartz SM, Chen C,**

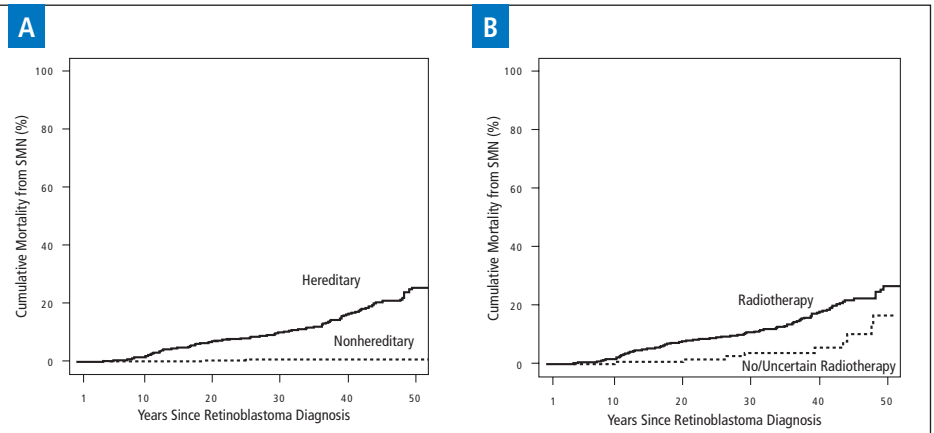


Figure 2. Cumulative mortality due to subsequent malignant neoplasms following diagnosis of retinoblastoma. (A) Cumulative mortality by hereditary status. (B) Cumulative mortality among hereditary retinoblastoma survivors by radiotherapy status. SMN = subsequent malignant neoplasm. (Yu CL, et al. 2009)

Neto JE, Wünsch-Filho V, Zaridze D, Koifman S, Curado MP, Benhamou S, Matos E, Szeszenia-Dabrowska N, Olshan AF, Lence J, Menezes A, Daudt AW, Mates IN, Pilarska A, Fabianova E, Rudnai P, Winn D, Ferro G, Brennan P, Boffetta P, Hayes RB. Type of alcoholic beverage and risk of head and neck cancer—a pooled analysis within the INHANCE Consortium. ***Am J Epidemiol*** **2009;169:132–142)**

LEUKEMIA

Early Chronic Lymphocytic Leukemia Markers

The authors examined whether chronic lymphocytic leukemia (CLL) was always preceded by monoclonal B-cell lymphocytosis (MBL) among 77,469 healthy adults who were enrolled in the PLCO Cancer Screening Trial. Forty-five subjects in whom CLL was diagnosed up to 6.4 years later were identified. Through analysis of peripheral blood samples and use of six-color flow cytometry (with antibodies CD45, CD19, CD5, CD10, kappa, and lambda) and immunoglobulin heavy-chain gene rearrangement by reverse-transcriptase polymerase-chain-reaction assay, the association between MBL and subsequent CLL was determined and the immunoglobulin gene repertoire of the prediagnostic B-cell clones characterized. On the basis of either flow-cytometric or molecular analysis, 44 of 45 patients with CLL had a prediagnostic B-cell clone; in 91% of patients, the presence of the B-cell clone was confirmed by both methods. The presence of immunoglobulin heavy-chain variable (*IgVH*) genes was determined in 78% of prediagnostic clones. Of these clones, 46% were *IgVH*3 subgroup genes (including 17% *IgVH*3-23 genes), and 26% were *IgVH*4 subgroup genes (including 11% *IgVH*4-34 genes). Seventy-seven percent of the *IgVH* sequences had mutations. **(Landgren O, Albitar M, Ma W, Abbasi F, Hayes RB, Ghia P, Marti GE, Caporaso NE. B-cell clones as early markers for chronic lymphocytic leukemia.** ***N Engl J Med*** **2009;360:659–667)**

LUNG CANCER

Red Meat, Processed Meat, and Meat Mutagens

The association of red meat, processed meat, and meat mutagen intake with lung cancer risk was investigated among 1,903 cases and 2,073 controls in the Environment and Genetics in Lung Cancer Etiology study, a population-based case-control study. Red and processed meat were positively associated with lung cancer risk (highest vs. lowest tertile: ORs = 1.8 and 1.7, respectively); the risks were strongest among never smokers (ORs = 2.4 and 2.5, respectively). Intakes of heterocyclic amines (HCAs) and benzo(a)pyrene were also associated with increased risk. Significant positive associations for both meat groups were found for adenocarcinoma and squamous cell carcinoma but not for small cell carcinoma. **(Lam TK, Cross AJ, Consonni D, Randi G, Bagnardi V, Bertazzi PA, Caporaso NE, Sinha R, Subar AF, Landi MT. Intakes of red meat, processed meat, and meat mutagens increase lung cancer risk.** ***Cancer Res*** **2009;69:932–939)**

LYMPHOMA

Organochlorine Exposure and Immune Gene Variation

To examine whether an association between organochlorine exposure and non-Hodgkin lymphoma (NHL) is modified by immune gene variation, the authors genotyped 61 polymorphisms in 36 immune genes among 1,172 NHL cases and 982 controls. They examined three exposures with elevated risk: PCB180 (plasma, dust measurements), the toxic equivalency quotient (an integrated functional measure of several organochlorines) in plasma, and alpha-chlordane (dust measurements, self-reported termiticide use). Associations between all three exposures and NHL risk were limited to the same genotypes for *IFNG* (C-1615T) (TT) and *IL4* (5′-UTR, Ex1-168C>T) (CC) (see Figure 3). Associations between PCB180 in plasma and dust and NHL risk were limited to the same genotypes for *IL16* (3′-UTR, Ex22+871A>G) (AA), *IL8* (T-251A) (TT), and *IL10* (A-1082G) (AG/GG). This provides one of the first examples of a potential gene-environment interaction for NHL. **(Colt JS, Rothman N, Severson RK, Hartge P, Cerhan JR, Chatterjee N, Cozen W, Morton LM, De Roos AJ, Davis S, Chanock S, Wang SS. Organochlorine exposure, immune gene variation, and risk of non-Hodgkin lymphoma.** ***Blood*** **2009;113:1899–1905)**

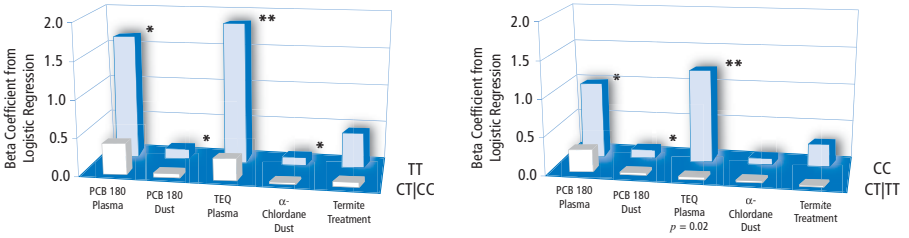


Figure 3. Exposure to five measures of organochlorine exposure and NHL risk, stratified by genotype. (A) *IFNG* C–1615T and (B) *IL4* 5'-UTR, Ex1–168T. * denotes $p < 0.05$. ** denotes $p < 0.01$. p value accompanies x-axis label if there is a significant interaction (p for interaction < 0.05) between genotype and exposure; y-axis is β coefficient from logistic regression. (Colt JS, et al. 2009)

MULTIPLE MYELOMA

Previous Monoclonal Gammopathy of Undetermined Significance

The frequency with which multiple myeloma (MM) is preceded by a premalignant asymptomatic monoclonal gammopathy of undetermined significance (MGUS) was assessed among 77,469 healthy adults enrolled in the PLCO Cancer Screening Trial. Seventy-one individuals who developed MM during the course of the study and had serially collected (up to six) pre-diagnostic serum samples obtained 2–9.8 years prior to MM diagnosis were identified. Using assays for monoclonal (M)-proteins and kappa-lambda free light chains (FLC), MGUS was present in 100%, 98.3%, 97.9%, 94.6%, 100%, 93.3%, and 82.4% at 2, 3, 4, 5, 6, 7, and 8+ years prior to MM diagnosis, respectively. In about half the study population, the M-protein concentration and involved FLC-ratio levels showed a yearly increase prior to MM diagnosis. **(Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, Dispenzieri A, Kumar S, Clark RJ, Baris D, Hoover R, Rajkumar SV. Monoclonal gammopathy of undetermined significance (MGUS) precedes multiple myeloma: a prospective study. *Blood* 2009;113:5412–5417)**

Familial Risks Associated with MGUS

Using data from Sweden, the authors identified 4,458 MGUS patients, 17,505 population-based controls, and first-degree relatives of patients (n = 14,621) and controls (n = 58,387). Compared with relatives of controls, relatives of MGUS patients had increased risk of MGUS (RR = 2.8), MM (RR = 2.9), lymphoplasmacytic lymphoma/Waldenström's macroglobulinemia (LPL/WM) (RR = 4.0), and CLL (RR = 2.0). Relatives of patients with IgG/IgA MGUS had a 4.0-fold, 2.9-fold, and 20-fold elevated risk of developing MGUS, MM, and LPL/WM, respectively. Relatives of IgM MGUS patients had a 5.0-fold increased CLL risk and nonsignificant excess MM and LPL/WM risks. The results were very similar when risks were assessed by type of first-degree relative, age at MGUS (above/below 65 years), and sex. Risk of NHL or Hodgkin lymphoma was not increased among MGUS relatives. **(Landgren O, Kristinsson SY, Goldin LR, Caporaso NE, Blimark C, Mellqvist UH, Wahlin A, Bjorkholm M, Turesson I. Risk of plasma-cell and lymphoproliferative disorders among 14,621 first-degree relatives of 4,458 patients with monoclonal gammopathy of undetermined significance (MGUS) in Sweden. *Blood* 2009; Jan 30 [E-pub ahead of print])**

OVARIAN CANCER

TP53 Gene Variants

The authors assessed whether polymorphisms in the region encoding *TP53* were associated with risk of invasive ovarian cancer. The study population included 5,206 invasive ovarian cancer cases (2,829 of which were serous) and 8,790 controls from 13 studies participating in the Ovarian Cancer Association Consortium (OCAC). Three of the studies performed independent discovery investigations involving genotyping of up to 23 SNPs in the *TP53* region. Significant findings from this discovery phase were followed up for replication in the other OCAC studies. Five SNPs showed significant associations with risk in one or more of the discovery investigations and were followed up by OCAC. Mixed effects analysis confirmed associations with serous invasive cancers for two correlated (r^2 = 0.62) SNPs: rs2287498 (median per allele OR = 1.30) and rs12951053 (median per allele OR = 1.19). Analyses of other histologic subtypes suggested similar associations with endometrioid but not with mucinous or clear cell cancers. **(Schildkraut JM, Goode EL, Clyde MA, Iversen ES, Moorman PG, Berchuck A, Marks JR, Lissowska J, Brinton L, Peplonska B, Cunningham JM, Vierkant RA, Rider DN, Chenevix-Trench G, Webb PM, Beesley J, Chen X, Phelan C, Sutphen R, Sellers TA, Pearce L, Wu AH, Van Den Berg D, Conti D, Elund CK, Anderson R, Goodman MT, Lurie G, Carney ME, Thompson PJ, Gayther SA, Ramus SJ, Jacobs I, Krüger Kjaer S, Hogdall E, Blaakaer J, Hogdall C, Easton DF, Song H, Pharoah PD, Whittemore AS, McGuire V, Quaye L, Anton-Culver H, Ziogas A, Terry KL, Cramer DW, Hankinson SE, Tworoger SS, Calingaert B, Chanock S, Sherman M, Garcia-Closas M; Australian Ovarian Cancer Study Group. Single nucleotide polymorphisms in the *TP53* region and susceptibility to invasive epithelial ovarian cancer. *Cancer Res* 2009;69:2349–2357)**

PROSTATE CANCER

Adipokine Gene Effects

Common variants of the *IL6, LEP, LEPR, TNF,* and *ADIPOQ* genes were examined among 1,053 prostate cancer cases and 1,053 controls in a large cohort of Finnish men. The authors also examined genotypes in relation to serum insulin, IGF-1, and IGF-1:IGFBP-3 among 196 controls. Variant alleles at three loci (–14858A>G, –13973A>C, –13736C>A) in a potential regulatory region of the *LEP* gene conferred a 20% reduced risk of prostate cancer. At the –14858A>G locus, heterozygotes and homozygotes for the A allele had an OR for prostate cancer of 0.76 and 0.79, respectively. At 13288G>A, relative to the GG genotype, the AA genotype was associated with a suggestive increased risk of prostate cancer (OR = 1.29; confidence interval = 0.99–1.67; *p* for trend = 0.05). Polymorphisms in the *IL6, LEPR, TNF,* and *ADIPOQ* genes were not associated with prostate cancer. The association of the allelic variants in the *LEP* gene with prostate cancer risk supports a role for leptin in prostate carcinogenesis. **(Moore SC, Leitzmann MF, Albanes D, Weinstein SJ, Snyder K, Virtamo J, Ahn J, Mayne ST, Yu H, Peters U, Gunter MJ. Adipokine genes and prostate cancer risk. *Int J Cancer* 2009;124:869–876)**

Metabolizing Genes and HCAs

Genetic data from the PLCO Cancer Screening Trial were used to determine if prostate cancer risks associated with dietary HCAs (2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine [PhIP]; 2-amino-3,8-dimethylimidazo[4,5-b] quinoxaline [MeIQx]; and 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline [DiMeIQx]) from cooked meat were modified by SNPs in genes involved in HCA metabolism (*CYP1A1, CYP1A2, CYP1B1, GSTA1, GSTM1, GSTM3, GSTP1, NAT1, NAT2, SULT1A1, SULT1A2,* and *UGT1A* loci). The study included 1,126 prostate cancer cases and 1,127 controls selected for GWAS for prostate cancer. The strongest evidence for an interaction was noted between DiMeIQx and MeIQx and the polymorphism rs11102001 downstream of the *GSTM3* locus. Among men carrying the A variant, the risk of prostate cancer associated with high DiMeIQx intake was 2.3-fold greater than that with low intake. HCAs may act as promoters of malignant transformation by altering mitogenic signaling. **(Koutros S, Berndt SI, Sinha R, Ma X, Chatterjee N, Alavanja MC, Zheng T, Huang WY, Hayes RB, Cross AJ. Xenobiotic metabolizing gene variants, dietary heterocyclic amine intake, and risk of prostate cancer. *Cancer Res* 2009;69:1877–1884)**

SKIN CANCER

AIDS and Nonkeratinocytic Skin Cancer

The authors linked data from U.S. AIDS and cancer registries to evaluate risk of nonkeratinocytic skin cancers (melanoma, Merkel cell carcinoma (MCC), and appendageal carcinomas, including sebaceous carcinoma [SC]) in 497,142 persons with AIDS. From 60 months before to 60 months after AIDS onset, persons with AIDS had elevated risks of melanoma (standardized incidence ratio [SIR] = 1.3), MCC (SIR = 11), and SC (SIR = 8.1). Risk for appendageal carcinomas increased with progressive time relative to AIDS onset. Risk of these skin cancers was higher among non-Hispanic whites than among other racial/ethnic groups, and melanoma risk was highest among men who had sex with men. Melanoma risk was unrelated to CD4 cell count at AIDS onset. Risks for melanoma and appendageal carcinomas rose with increasing exposure to ultraviolet radiation. The greatly increased risks for MCC and SC suggest an etiologic role for immunosuppression. **(Lanoy E, Dores GM, Madeleine MM, Toro JR, Fraumeni JF Jr, Engels EA. Epidemiology of nonkeratinocytic skin cancers among persons with AIDS in the United States. *AIDS* 2009;23:385–393)**

SC and Related Cancer Risks

Sebaceous tumors of the skin occurring in association with an internal malignancy characterize Muir-Torre syndrome (MTS), a variant of hereditary nonpolyposis colon cancer (Lynch syndrome). The authors calculated cutaneous SC incidence rates (IRs) and IR ratios in nine U.S. Surveillance, Epidemiology, and End Results program registries (1973 to 2003). Among 664 cases of cutaneous SC, nearly 90% were diagnosed among whites (IR = 0.11 per 100,000 person-years), with significantly lower IR noted among blacks (IR = 0.04). Whereas eyelid SC IRs demonstrated no sex differences and stabilized in recent years, IRs of non-eyelid SC predominated in men and rose steadily over time. Survivors of SC had a 43% increased risk of subsequent cancer, and risk of SC was 52% higher among survivors of other cancers. Whether before or after SC, the significant excesses of other primary cancers were limited to non-eyelid SC cases. Patterns suggestive of genetic predisposition included more than 20-fold risks for early-onset SC associated with colon, pancreatic, ovarian, or uterine corpus cancers, whereas late-onset SC predisposed to ureter cancer. This population-based study of cutaneous SC revealed an association with a spectrum of early-onset cancers consistent with MTS. **(Dores GM, Curtis RE, Toro JR, Devesa SS, Fraumeni JF Jr. Incidence of cutaneous sebaceous carcinoma and risk of associated neoplasms: Insight into Muir-Torre syndrome. *Cancer* 2008;113:3372–3381)**

THYROID CANCER

Thyroid Disease after *In Utero* I-131 Exposure

The authors present estimated risks of thyroid disease from exposure *in utero* to I-131 fallout from the Chernobyl nuclear accident. They conducted a cross-sectional thyroid screening study from 2003 to 2006 among 2,582 mother-child pairs from Ukraine in which the mother had been pregnant at the time of the accident on April 26, 1986, or up to about two months after the accident, when I-131 fallout was still present (1,494 from contaminated areas, 1,088 in the comparison group). Individual cumulative *in utero* thyroid dose estimates were derived from estimated I-131 activity in the mother's thyroid (mean 72 mGy; range 0–3230 mGy). There were seven cases of thyroid carcinoma and one case of Hurthle cell neoplasm identified as a result of the screening. The estimated excess OR per gray for thyroid carcinoma was nonsignificantly elevated (excess OR per gray = 11.66). No radiation risks were identified for other thyroid diseases. Results support a conservative approach to medical uses of I-131 during pregnancy. **(Hatch M, Brenner A, Bogdanova T, Derevyanko A, Kuptsova N, Likhtarev I, Bouville A, Tereshchenko V, Kovgan L, Shpak V, Ostroumova E, Greenebaum E, Zablotska L, Ron E, Tronko M. A screening study of thyroid cancer and other thyroid diseases among individuals exposed *in utero* to iodine-131 from Chernobyl fallout. *J Clin Endocrinol Metab* 2009;94:899–906)**

DCEG PEOPLE IN THE NEWS

In February, **Christian C. Abnet, Ph.D., M.P.H.,** Nutritional Epidemiology Branch (NEB), gave a talk on "Etiology of esophageal squamous cell carcinoma in Eastern and Western populations" at Queen's University in Belfast, Northern Ireland.

Blanche P. Alter, M.D., M.P.H., Clinical Genetics Branch (CGB), gave talks on inherited bone marrow failure syndromes at St. Joseph's Hospital in Paterson, New Jersey, in January; Stanford School of Medicine and Lucile Packard Children's Hospital in February; and the 10th Annual Diamond Blackfan Anemia International Consensus Conference in New York City in March.

In February, **Louise A. Brinton, Ph.D.,** Chief of the Hormonal and Reproductive Epidemiology Branch (HREB), gave a seminar on "Infertility and associated treatments and subsequent risk of cancer" at the National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina.

In March, **Neil E. Caporaso, M.D.,** Genetic Epidemiology Branch (GEB), spoke on "A genome-wide association study of smoking" at the International Lung Cancer Consortium meeting in Paris.

In April, **Joanne S. Colt, M.P.H., M.S.,** Assistant Branch Chief of the Occupational and Environmental Epidemiology Branch, gave an invited talk on "Bladder cancer in New England: Etiology and survival" at the Northeastern Genitourinary Oncology Symposium in Burlington, Vermont.

In January, **Sanford M. Dawsey, M.D.** (NEB), gave a talk on "Precursor lesions and primary screening techniques for esophageal squamous cell carcinoma" at the Second Beijing International Workshop on Early Detection and Treatment of Gastrointestinal Tumors held in China.

In March, **Mitchell H. Gail, M.D., Ph.D.,** Biostatistics Branch (BB), spoke on "The value of adding single nucleotide polymorphism data to a model that predicts breast cancer risk" as a keynote speaker at the Conference on Statistical Methods for Complex Data: In Honor of Raymond J. Carroll in College Station, Texas.

In January, **Li Jiao, M.D., Ph.D.** (NEB), gave a talk on "Gene, diet, lifestyle and risk of pancreatic cancer" at the Dan Duncan Cancer Center at the Baylor College of Medicine in Houston.

In March, **Mitchell H. Gail, M.D., Ph.D.,** a senior investigator in the Biostatistics Branch, received the 2009 Distinguished Achievement Award from the American Society of Preventive Oncology at its annual meeting in Tampa. Established in 1983, this award recognizes individuals whose research has significantly advanced cancer prevention and control. In honor of this award, Dr. Gail gave an invited lecture on "Risk models in cancer prevention."

Mitchell Gail (right) receives award from James Marshall, president of the American Society of Preventive Oncology.

In March, **Hormuzd A. Katki, Ph.D.** (BB), gave a talk on "Insights into *p*-values and Bayes factors from false positive and false negative Bayes factors" at the Department of Mathematics at the University of Maryland, College Park.

In March, **James V. Lacey, Jr., Ph.D.** (HREB), gave a seminar on "Progression from endometrial hyperplasia to carcinoma: Predictors, problems, and possibilities" at the Fred Hutchinson Cancer Research Center in Seattle.

In March, **Maria Teresa Landi, M.D., Ph.D.** (GEB), spoke on "MicroRNA expression in lung cancer" at the University of Milan. The same month, she gave a talk titled "A genome-wide association study of lung cancer" at the International Lung Cancer Consortium meeting in Paris.

In April, **Mary Lou McMaster, M.D.** (GEB), gave a talk on "Familial Waldenström's macroglobulinemia" at the International Waldenström's Macroglobulinemia Foundation Educational Forum in Memphis.

Marianne K. Henderson, M.S., Chief of the Office of Division Operations and Analysis, has been elected to serve a three-year term on the governing council for the International Society for Biological and Environmental Repositories (ISBER). ISBER is the leading international forum for addressing the technical, legal, ethical, and managerial issues relevant to repositories of biological and environmental specimens. As a councilor, Ms. Henderson will work to establish policies and procedures consistent with the missions of ISBER as well as to implement scientific meetings to achieve these aims.

Marianne Henderson

In March, **Melissa Rotunno, Ph.D.** (GEB), gave a talk on "Phase I metabolic genes and risk of lung cancer: Multiple polymorphisms and mRNA expression" at the NCI Center for Cancer Research's Ninth Annual Fellows and Young Investigators Colloquium in Hershey, Pennsylvania.

In February, **Sharon A. Savage, M.D.** (CGB), gave a talk on "Clinical and molecular characterization of dyskeratosis congenita, a cancer predisposition syndrome" at the meeting Pediatric Cancer Genetics: From Gene Discovery to Cancer Screening at Texas Children's Cancer Center in Houston.

In March, **Arthur Schatzkin, M.D., Dr.P.H.** (Chief of NEB), gave two lectures — "Can nutrition really cause and prevent cancer? (And can new -omics and internet technologies help answer the question?)" at Imperial College, London, and "Validation and qualification of surrogate end points: A cancer perspective" at a workshop held by the Institute of Medicine's Committee on Qualification of Biomarkers as Surrogate Endpoints in Chronic Disease Risk in Washington, DC.

In April, **Philip R. Taylor, M.D., Sc.D.** (GEB), spoke on "Esophageal cancer: Epidemiology and prevention" at the George Washington University School of Public Health and Health Services in Washington, DC. During the same month, he also gave a talk titled "SELECT: What next?" at the Experimental Biology Meeting, Selenium Session, in New Orleans.

In March, **Kai Yu, Ph.D.** (BB), gave an invited talk, "Stratification, evaluation, and adjustment in genome-wide association studies," at the Eastern North American Region of the International Biometric Society Meeting in San Antonio.

Louise Brinton receives award from Andrew Olshan, chair of the Department of Epidemiology at the University of North Carolina School of Public Health.

In February, **Louise A. Brinton, Ph.D.,** Chief of the Hormonal and Reproductive Epidemiology Branch, received the Herman Alfred Tyroler Distinguished Alumni Award of the University of North Carolina (UNC) School of Public Health (SPH). In accepting the award, Dr. Brinton gave an invited lecture titled "How findings regarding exogenous hormones have clarified our understanding of breast carcinogenesis." The award, established in 1975 as the school's single highest alumni honor, recognizes the achievements of alumni and their contributions to public health, including leadership, experimentation, collaboration, and innovation within the profession; impact within the practice arena; and outstanding service beyond the requirements of the recipient's employment. Dr. Brinton is a 1972 M.P.H. graduate of UNC SPH.

COMINGS . . . GOINGS


Hannah Arem

Hannah Arem, M.H.S., has joined DCEG's Office of Communications and Special Initiatives as an NCI Health Communications Intern. She received an M.H.S. degree from the Johns Hopkins Bloomberg School of Public Health, where she focused on international health. Previously, she worked for an international nonprofit organization that operates primary care clinics in developing countries, and she also worked on the National Diabetes Education Program, a joint program of the Centers for Disease Control and Prevention, NIH, and more than 200 partners. Through her six-month internship with DCEG, she will work with **Jennifer K. Loukissas, M.P.P.,** on numerous communications initiatives, including translation of scientific findings into practical and accessible public health messages.

Parveen Bhatti, Ph.D., M.S., a fellow in the Radiation Epidemiology Branch, left in January to take a position in the Epidemiology Program of the Public Health Sciences Division at the Fred Hutchinson Cancer Research Center in Seattle.

Victoria M. Chia, Ph.D., M.P.H., a postdoctoral fellow in the Hormonal and Reproductive Epidemiology Branch (HREB), has taken a position at Amgen, Inc., in Thousand Oaks, California. While in HREB, Dr. Chia worked on studies of testicular and endometrial cancer.


Kathryn Hughes

Kathryn Hughes, M.P.H., has joined the Occupational and Environmental Epidemiology Branch (OEEB) as a predoctoral fellow under the Yale University-NCI Partnership Training Program. Ms. Hughes will be working with **Michael C. R. Alavanja, Dr.P.H.** (OEEB); **Jay H. Lubin, Ph.D.,** Biostatistics Branch (BB); members of the Agricultural Health Study team; and her mentors from Yale, Drs. Tongzhang Zheng and Xiaomei Ma. She will conduct research on the effects of pesticides and genetic susceptibility on cancer.


Tamra Meyer

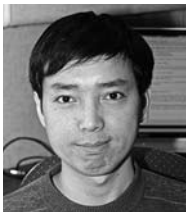
Tamra Meyer, Ph.D., has joined HREB as a postdoctoral Sallie Rosen Kaplan Fellow. Dr. Meyer received her Ph.D. in epidemiology from the University of Texas Health Science Center at Houston School of Public Health, where she studied relationships between genetic variation and chronic diseases. She is working with **Ann W. Hsing, Ph.D.,** on the molecular epidemiology of prostate and biliary tract cancers.

In February, **Elisabetta Petracci, M.Sc.,** joined BB and the Clinical Genetics Branch (CGB) as a predoctoral fellow. Ms. Petracci is completing her Ph.D. in biomedical statistics from the Institute of Medical Statistics and Biometry "Giulio A. Maccacaro," University of Milan. She will be working with **Mitchell H. Gail, M.D., Ph.D.** (BB), **Mark H. Greene, M.D.** (Chief of CGB), and her advisor from the University of Milan, Dr. Adriano Decarli, on projecting breast cancer risk, with a focus on mammographic density, modifiable risk factors, and analytic methods.


Elisabetta Petracci


Ingrid Wentzensen

Ingrid Wentzensen, M.D., has joined CGB as a postdoctoral fellow. She received her M.D. from Heidelberg University in Germany and has completed four years of general surgery residency, with a strong focus on surgical oncology, at the University Hospital of Heidelberg and the General Hospital of Weinheim. Dr. Wentzensen has a special interest in hereditary cancer syndromes and will be working with **Sharon A. Savage, M.D.,** on the epidemiology of Ewing sarcoma, studies of telomere biology and cancer genetic risk factors, and genetic studies of Li-Fraumeni syndrome.


Hong Zhang

Hong Zhang, Ph.D., has joined BB as a postdoctoral fellow. Dr. Zhang received his Ph.D. in statistics at the University of Science and Technology of China, where he also served as a faculty member. He also has had postdoctoral training at both Yale University and George Washington University. He will be working with **Kai Yu, Ph.D.,** on developing new statistical methods that address challenges from genetic association studies.

DIRECTOR RECEIVES LIFETIME ACHIEVEMENT AWARD

In April, **Joseph F. Fraumeni, Jr., M.D.,** Division Director, received the American Association for Cancer Research (AACR) Award for Lifetime Achievement in Cancer Research in recognition of his seminal contributions to understanding the causes and prevention of human cancer. Established in 2004, this award honors an individual who has made lasting and significant fundamental contributions to cancer research, either through a single scientific discovery or a body of work, and has demonstrated a lifetime commitment to progress against cancer.

Dr. Fraumeni's many accomplishments include the discovery and characterization of Li-Fraumeni syndrome, which bears his name along with that of his colleague Dr. Frederick P. Li, as well as the development of the U.S. Cancer Mortality Atlas project, which uses color-coded maps of cancer mortality at the county level to display high-risk areas. Epidemiologic studies carried out in these areas have uncovered a number of previously unrecognized carcinogenic hazards, including associations between oral cancer and smokeless tobacco in the South, lung cancer and asbestos exposure along coastal areas, lung cancer and inhaled arsenic among smelter workers and residents of surrounding communities, lymphoma and the use of agricultural herbicides in farming communities, nasal cancer and work in the furniture industry in the Southeast, and bladder cancer and certain occupational exposures as well as high levels of arsenic in drinking water in the Northeast. Many of these studies have led to cancer control measures, including labeling policies and educational campaigns for smokeless tobacco and regulatory limits for arsenic exposure.

Dr. Fraumeni's epidemiological work has had a strong interdisciplinary orientation with clinical and laboratory components. He is the author of more than 800 scholarly papers and several books, and he continues to advance cancer research through his leadership and vision at the national and international levels. For more than 30 years,

AACR President-elect Elizabeth Blackburn and Joseph Fraumeni

Dr. Fraumeni has been the architect of NCI's research program in epidemiology, genetics, and related areas while developing fellowship programs designed to train and mentor the next generation of interdisciplinary scientists.

"I am delighted to receive this award, particularly as it comes from the world's leading professional society devoted to cancer research," Dr. Fraumeni said. ■

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