National Cancer Institute

DIVISION OF CANCER EPIDEMIOLOGY AND GENETICS

Linkage

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IN THIS ISSUE:

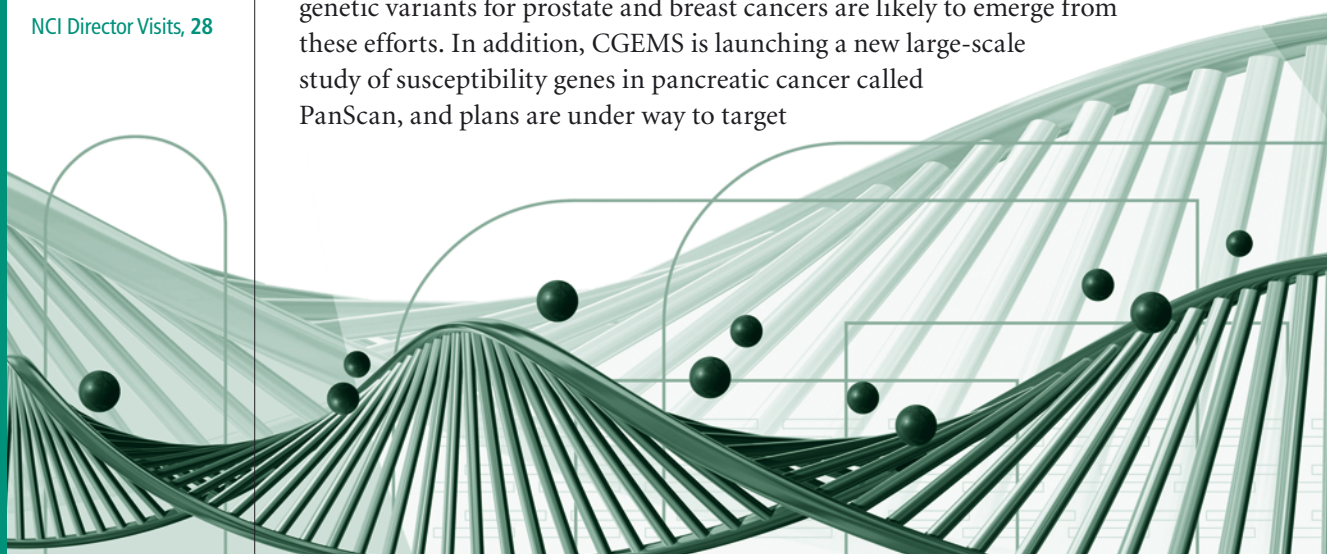
DIRECTOR'S PAGE

Genome-wide Association Studies: Next Steps

The recent development of technologies to harness the transformational knowledge and tools generated by the human genome and haplotype mapping projects has invigorated epidemiologic strategies to uncover the genetic contribution to complex diseases such as cancer. In 2007, the capacity to interrogate the entire human genome has resulted in a cascade of genome-wide association studies (GWAS) pointing to common single nucleotide polymorphisms (SNPs) that may raise or lower the risk for various forms of cancer. By scanning the DNA collected from individuals participating in large-scale cohort or case-control studies, researchers can identify highly significant associations with candidate SNPs, which are then validated (while false positives are discarded) through a coordinated series of replication studies involving independent study populations.

The NCI Cancer Genetic Markers of Susceptibility (CGEMS) project illustrates the promise of this approach, through which investigators recently pinpointed genetic regions or loci associated with the risk of prostate and breast cancers using resources from the NCI Cohort Consortium along with case-control studies. Based on intramural and extramural partnerships of epidemiologists and genomicists, the CGEMS initiative began by scanning the germline DNA of thousands of prostate cancer cases, as compared to that of healthy men. The main finding to date has been the detection of multiple SNPs associated with the risk of prostate cancer in a previously unsuspected region of chromosome 8q24 (*Nature Genetics* 2007;39:645–649). In a parallel CGEMS study, breast cancer risk was related to common genetic variants in *FGFR2* (fibroblast growth factor receptor 2) as well as to variants in the 8q24 region (*Nature Genetics* 2007;39:870–874).

Both studies are moving into comprehensive replication stages, and several other genetic variants for prostate and breast cancers are likely to emerge from these efforts. In addition, CGEMS is launching a new large-scale study of susceptibility genes in pancreatic cancer called PanScan, and plans are under way to target



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Members of the New Laboratory of Translational Genomics: Jun Fang, Tammy Yeager, Stephen Chanock, Hye Kim, and Jesus Gonzalez-Bosquet. (Not shown: Renee Chen)

other cancers, including those of the lung, bladder, and kidney, as well as lymphoma. NCI's Core Genotyping Facility plays a key role in these initiatives through its high-throughput capacity to conduct whole-genome scans along with candidate gene searches to identify low- and medium-penetrant variants that affect cancer risk.

The discovery of signals in the 8q24 chromosomal region for prostate and breast cancers was surprising because this region appears devoid of known genes. Very recent data indicate that the 8q24 region is also involved in colon cancer and perhaps certain other tumors, suggesting that a novel mechanistic pathway of cancer susceptibility may be shared by a variety of cancers. Because of NCI's long-standing investment in intramural and extramural cohort and case-control studies with biospecimen collections, a wealth of germline DNA samples is already at hand and enables investigators to explore the 8q24 region in many forms of cancer.

Underpinning the success of these efforts has been the formation of large-scale international consortia involving a collaborative effort between DCEG and the Division of Cancer Control and Population Sciences. In particular, the Cohort Consortium currently totals more than 4 million subjects and includes extensive epidemiologic data along with biospecimens. In addition, several consortia based mainly on population- and hospital-based case-control studies have been established to investigate less common cancers that cannot be easily evaluated in cohort studies. Other international collaborations are focusing on familial cancer syndromes in which high-penetrant genes have eluded discovery or opportunities exist to identify genetic and environmental modifiers of inherited risk.

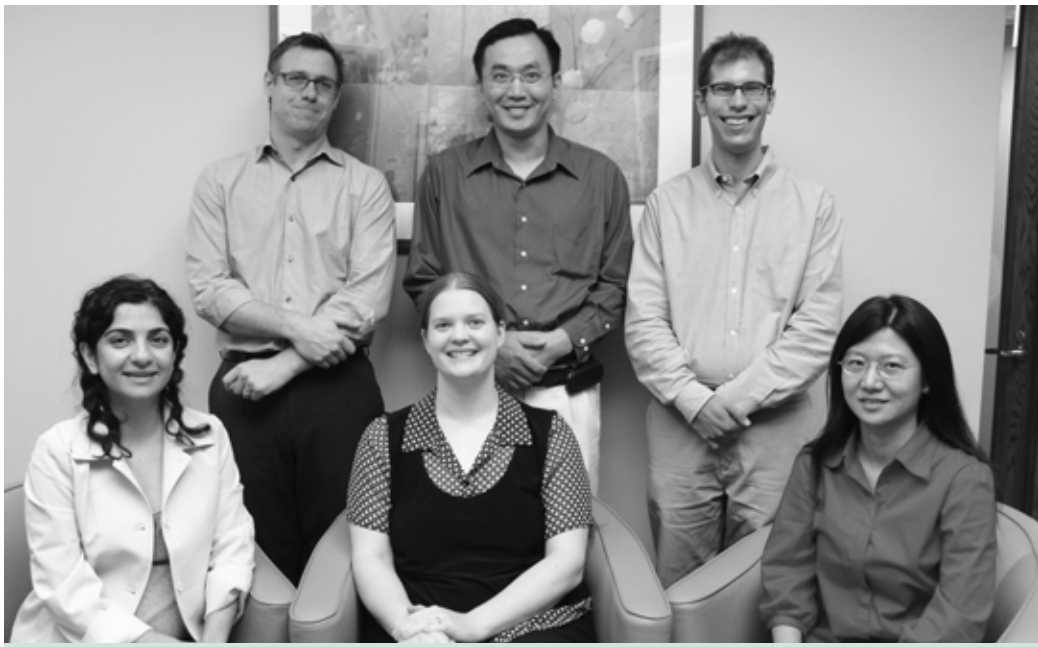
To capitalize on the emerging opportunities provided by GWAS, DCEG recently established a new Laboratory of Translational Genomics. Its objectives are to conduct fine-scale mapping and sequencing of established loci in well-defined biological samples derived from epidemiologic studies; perform methodological studies that enhance high-throughput genotyping and sequencing activities; characterize the genomic regions and markers associated with cancer susceptibility or resistance and collaborate with

epidemiologists, statisticians, and bioinformaticians to identify gene-gene and gene-environment interactions; and forge collaborations with basic and clinical scientists for functional and other biological studies to pinpoint causal gene variants and mechanisms that may guide the design of preventive, diagnostic, and therapeutic interventions.

In addition, DCEG is helping to develop an NCI Applied Molecular Pathology Core Laboratory that will carry out large-scale studies of gene expression and somatic mutations in tumor specimens collected as part of GWAS. The construction of tissue microarrays for high-throughput analysis will enable the molecular subclassification of cancers and allow differential risk-factor assessment for a variety of tumor subtypes. The approach will also relate the genomic and molecular alterations within tumors to the genetic variants identified by GWAS. This information will then be analyzed in the broader epidemiologic context designed to examine the interplay of genetic and environmental factors in tumor induction and progression.

To help facilitate a trans-NCI research program to pursue the leads generated by GWAS, a workshop was recently convened by DCEG and the Center for Cancer Research to discuss the methods and technologies needed for the discovery of functional genetic variants and mechanisms associated with cancer risk. Toward this end, NCI has created a center of excellence to foster multidisciplinary approaches that should accelerate the biological, epidemiologic, and statistical research informed by GWAS and its translation into new clinical and public health strategies. ■

—Joseph F. Fraumeni, Jr., M.D.



FARE Winners: (front) Mahboobeh Safaeian, Jill Koshiol, and Ying Gao; (back) Mark Purdue, Sheng Luo, and Neal Freedman. (Not shown: Elizabeth Bluhm)

NIH RECOGNIZES 2008 FARE WINNERS

The NIH Fellows Award for Research Excellence (FARE) program recognizes outstanding scientific research by intramural postdoctoral fellows. Fellows submit abstracts of their research, which are reviewed by a panel of NIH postdoctoral fellows as well as tenured and tenure-track investigators. Winners receive a $1,000 travel stipend to attend and present their work at a scientific meeting in the United States. This year, seven DCEG fellows each received an award.

DCEG Winners and Abstract Titles

- **Elizabeth C. Bluhm, M.D., M.P.H.,** Radiation Epidemiology Branch: *Cause-specific mortality and second cancer incidence after non-Hodgkin lymphoma in childhood.*
- **Neal D. Freedman, Ph.D., M.P.H.,** Nutritional Epidemiology Branch: *Menstrual and reproductive factors and gastric cancer risk in a large prospective study of women.*
- **Ying Gao, M.D., Ph.D., M.P.H.,** Genetic Epidemiology Branch (GEB): *Familial characteristics of celiac disease, autoimmunity, and subsequent risk of lymphoma.*
- **Jill Koshiol, Ph.D.** (GEB): *Patterns of autoimmunity and subsequent risk of Waldenström macroglobulinemia.*
- **Sheng Luo, Ph.D.,** Biostatistics Branch: *Analysis of smoking cessation patterns using a stochastic mixed effects model with a latent cured state.*
- **Mark Purdue, Ph.D.,** Occupational and Environmental Epidemiology Branch: *Serum organochlorine levels and risk of testicular germ cell tumors: A nested case-control study.*
- **Mahboobeh Safaeian, Ph.D.,** Hormonal and Reproductive Epidemiology Branch: *Risk of precancer and follow-up management strategies for women with human papillomavirus–negative, atypical squamous cells of undetermined significance.*

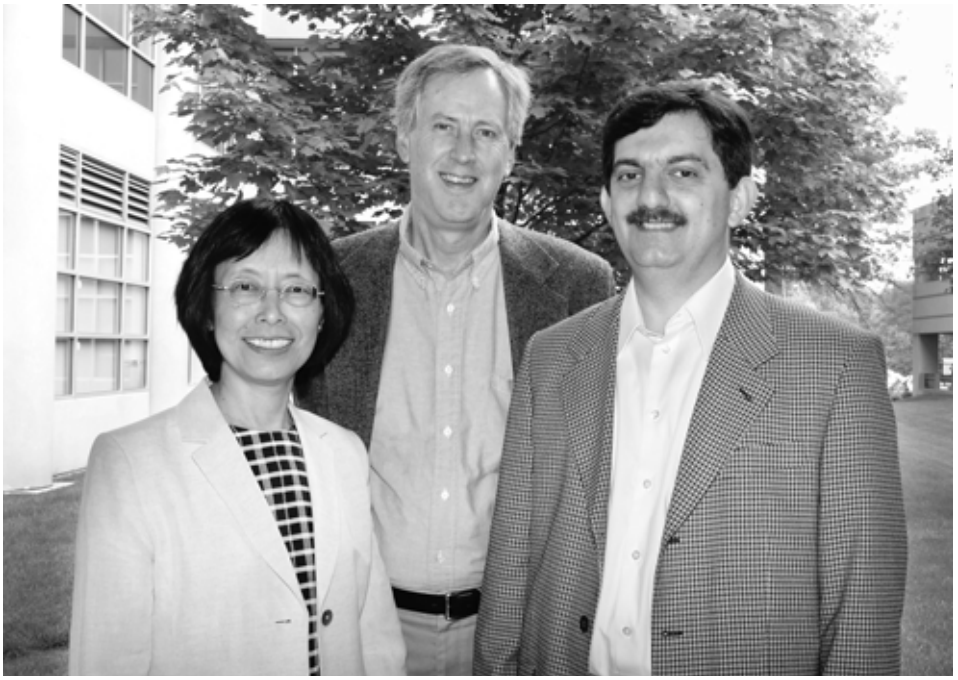
More information about the FARE competition is available at http://felcom.nih.gov/FARE.

WORKSHOP DISCUSSES NEW IDEAS FOR ESOPHAGEAL DISEASE RESEARCH

In May, the third annual meeting of the Barrett's Esophagus and Esophageal Adenocarcinoma Consortium (BEACON) was held in Bethesda, Maryland. **Wong-Ho Chow, Ph.D.,** Occupational and Environmental Epidemiology Branch, **Farin Kamangar, M.D., Ph.D.,** Nutritional Epidemiology Branch (NEB), and Dr. Thomas Vaughan of the Fred Hutchinson Cancer Research Center in Seattle were the organizers.

During a two-day workshop, supported by the NIH Office of Rare Diseases, 45 scientists convened to review current projects on esophageal adenocarcinoma (EA) and Barrett's esophagus (BE), to develop new research ideas and strategies, to share the latest developments in clinical methods and laboratory analyses that could be applied to consortium projects, and to discuss early results from pooled analyses. Participants represented NCI; the National Institute of Diabetes and Digestive and Kidney Diseases; the International Agency for Research on Cancer; and academic institutions in the United States, Canada, the United Kingdom, Sweden, Denmark, Australia, and Brazil.

Using data from seven different studies in the BEACON consortium, Dr. Kamangar, **Neal D. Freedman, Ph.D., M.P.H.** (NEB), and Dr. Carol Griffen of Information Management Services, Inc., developed a database for conducting pooled analyses. Preliminary results indicate a consistent dose-response association between smoking and EA as well as a suggestive association with alcohol intake. Dr. Deirdre Cronin-Fenton of Aarhus University in Denmark presented her findings on the role of reproductive factors, suggesting that endogenous hormones may influence the risk of EA in women.



Workshop Co-organizers: Wong-Ho Chow, Thomas Vaughan, and Farin Kamangar.

Dr. David Whiteman of the University of Queensland, Australia, noted, "It was worth every mile I traveled."

One session focused on the use of new technology, such as whole-genome scanning, in future research into genetic susceptibility. **Stephen J. Chanock, M.D.,** Director of the NCI Core Genotyping Facility and Chief of the Laboratory of Translational Genomics, discussed the potential for genome-wide association studies using BEACON resources. Another session addressed etiologic questions, such as obesity and the potential role of the hormones ghrelin and leptin; the possible protective effects of *Helicobacter pylori* in reflux esophagitis, BE, and EA; and reasons for gender and ethnic disparities in risk.

Progress reports were provided on projects using consortium resources, including a study of risk factors for BE among women, a study of genetic predisposition to BE and EA based on candidate gene searches and epigenetics, and a study of obesity and metabolic syndrome in EA along with serum insulin-like growth factors.

Participants praised the workshop as highly productive. Dr. David Whiteman of the University of Queensland, Australia, noted, "It was worth every mile I traveled."

The fourth workshop will be held in the spring of 2008. ■

NEW TRAVEL AWARD FOR FELLOWS ANNOUNCED

The DCEG Fellows Award for Research Excellence (D-FARE) is a new travel award to enhance the professional development of DCEG fellows. NIH FARE winners are not eligible to compete in the D-FARE competition.

This DCEG award, proposed by the Office of Education Advisory Group (OEAG) and sponsored by OE, recognizes scientific research projects conducted by DCEG fellows who have made exceptional contributions to a DCEG research study. This year, five D-FARE winners will receive $1,000 each for travel to present their research at a scientific meeting. Fellows must have made substantial contributions to a research project by formulating the idea, design, fieldwork, analysis, or interpretation of results, and had major participation in drafting a manuscript. Special consideration is given to projects in which fellows demonstrate growth beyond the discipline of their previous training.

Louise A. Brinton, Ph.D., Chair of OEAG and Chief of the Hormonal and Reproductive Epidemiology Branch, noted, "The OEAG recognizes that attendance at meetings is critical to the fellowship experience. This competition will allow greater numbers of fellows to attend meetings, allowing them to gather information on important new scientific developments and to make vital connections with other scientists."

A diverse group of DCEG scientists judged the submissions and made recommendations to the DCEG Director for final award determinations. Awards were announced in October, and funds must be used by the end of the fiscal year. ■

AND THE WINNERS ARE…

- **Laura E. Beane-Freeman, Ph.D.,** Occupational and Environmental Epidemiology Branch (OEEB): *Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries.*
- **Michael B. Cook, Ph.D.,** Hormonal and Reproductive Epidemiology Branch: *DNA damage and risk of testicular germ cell tumors.*

D-FARE Winners: Laura Beane-Freeman, Min Shen, Michael Cook, and James Li. (Not shown: Yan Li)

- **James (Qizhai) Li, Ph.D.,** Biostatistics Branch (BB): *Improved correction for population stratification in genome-wide association studies by identifying hidden population structures.*
- **Yan Li, Ph.D.** (BB): *Testing Hardy-Weinberg equilibrium and homogeneity of disequilibrium using complex survey data.*
- **Min Shen, M.D., Ph.D.** (OEEB): *Census and geographic differences between respondents and non-respondents in a case-control study of non-Hodgkin lymphoma.*

SOCIETY FOR EPIDEMIOLOGIC RESEARCH MEETS

At the 40th Annual Society for Epidemiologic Research Meeting in Boston this June, DCEG researchers made presentations, displayed posters, and moderated educational sessions on their work.

Louise A. Brinton, Ph.D., Chief of the Hormonal and Reproductive Epidemiology Branch (HREB), chaired a spotlight session on "Etiologic heterogeneity of breast cancer" and led a roundtable on "Are we making progress in understanding the etiology of breast cancer?" **An-Tsun Huang, Ph.D.,** Occupational and Environmental Epidemiology Branch (OEEB), gave an oral presentation at a late-breaking session on "Bladder cancer and reproductive factors," and **Mary H. Ward, Ph.D.** (OEEB), spoke at a symposium on "Using geographic information systems for exposure assessment in epidemiologic studies of cancer."

In spotlight sessions, **Mark E. Sherman, M.D.** (HREB), spoke on the "Application of tissue microarrays in molecular epidemiologic research: Getting to the core of the matter," and **Rajeev Mahajan, M.H.S.** (OEEB), spoke on "Carbaryl exposure and incident cancer in the Agricultural Health Study."

Sonja I. Berndt, Pharm.D., Ph.D. (OEEB), won Second Place for her poster on "Disparities in survival between black and white patients with renal cell cancer."

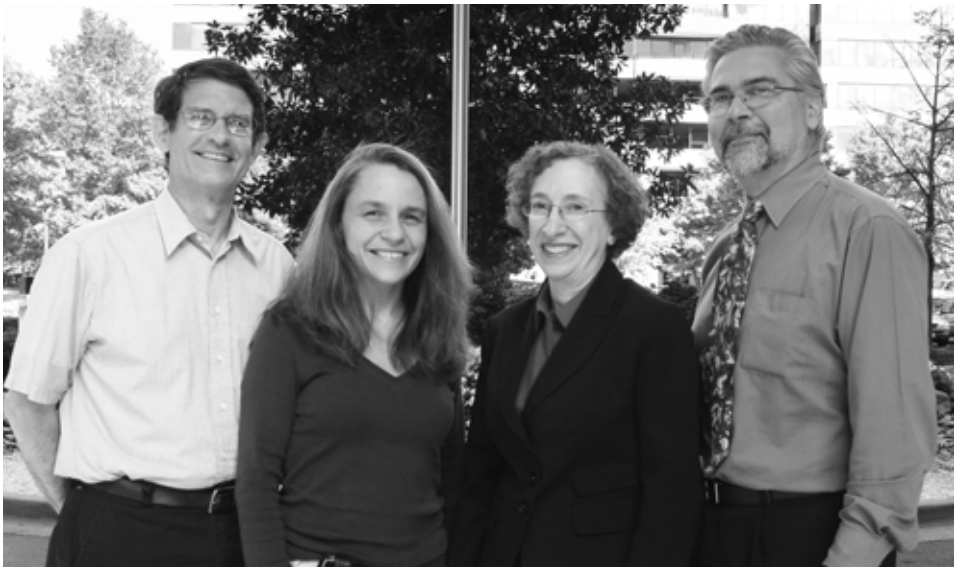
Other DCEG presenters included **Gretchen L. Gierach, Ph.D., M.P.H.** (HREB), who presented "Non-steroidal anti-inflammatory drugs and breast cancer risk in the NIH-AARP Diet and Health Study"; **Jill Koshiol, Ph.D.** (GEB), who spoke on "Epstein-Barr virus serology and gastric cancer incidence and survival"; **Claudine M. Samanic, M.S.P.H.** (OEEB), who delivered "Occupational exposure to pesticides and risk of brain tumors"; and **Stephanie J. Weinstein, Ph.D.** (NEB), who presented "Serum markers of one-carbon metabolism and risk of colorectal cancer."

DCEG STAFF WIN NIH MERIT AWARDS

In November, several DCEG staff members were recognized for their accomplishments at the annual NIH Awards Ceremony. NCI Director John E. Niederhuber, M.D., presented NIH Merit Awards to the following staff members:

- **Rochelle E. Curtis, M.A., D. Michal Freedman, Ph.D., M.P.H.,** and **Elaine Ron, Ph.D.,** of the Radiation Epidemiology Branch (REB), **Margaret A. Tucker, M.D.,** Director of the Human Genetics Program and Chief of the Genetic Epidemiology Branch, **Alyssa Minutillo, M.P.H.,** Office of the Director, and **Joseph F. Fraumeni, Jr., M.D.,** Director of DCEG, along with Lynn A.G. Ries and Brenda K. Edwards (Division of Cancer Control and Population Sciences) as well as David G. Hacker (Information Management Services, Inc.), for their landmark second cancers study, the first systematic assessment in the United States of multiple cancer risk among 2 million cancer survivors.
- **Steven L. Simon, Ph.D., André Bouville, Ph.D., Ruth A. Kleinerman, M.P.H., Kathleen Stine, M.B.A.,** and Dr. Ron (REB) for the first broad-based description of applications of radiation dosimetry to epidemiological studies—an invaluable international resource.
- **Louise A. Brinton, Ph.D.,** Chief of the Hormonal and Reproductive Epidemiology Branch (HREB), for her direction of the Branch, which combines scientific leadership, administrative excellence, and caring mentorship.
- **Philip E. Castle, Ph.D.** (HREB), for his leadership in guiding the translation of human papillomavirus vaccine testing into cervical cancer screening in low-resource areas of the United States.
- Ms. Kleinerman for discovering the first evidence of gene-radiation interactions underlying excess risks of multiple types of subsequent cancers among retinoblastoma patients.

Ruth Kleinerman, Philip Castle, and Louise Brinton.



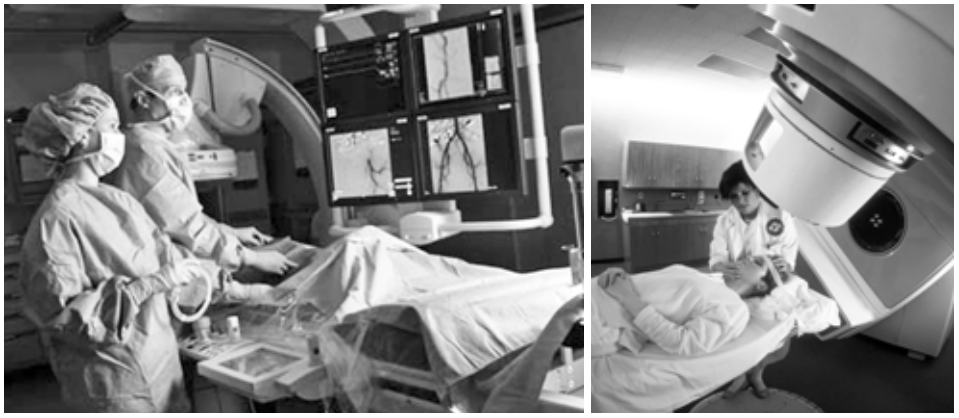
Sanford Dawsey, Montserrat García-Closas, Martha Linet, and Demetrius Albanes.

In addition, **Demetrius Albanes, M.D.,** Chief of the Office of Education and a senior investigator in the Nutritional Epidemiology Branch (NEB), received an NCI Outstanding Mentor Award for his contribution to a critical element of DCEG's mission—training the next generation of scientists. The winners of this award are nominated by NCI postdoctoral fellows.

Sanford M. Dawsey, M.D. (NEB), **Montserrat García-Closas, M.D., Dr.P.H.** (HREB), and **Martha S. Linet, M.D., M.P.H.** (Chief of REB), also received NCI Mentors of Merit Awards. ■

POTENTIAL RISKS OF NEW RADIATION TECHNOLOGIES

A priority of the Radiation Epidemiology Branch (REB) is to assess the risks associated with burgeoning technologies that potentially expose patients and health care providers to the adverse effects of ionizing radiation. Although many of these technologies provide significant advantages in detecting numerous diseases and treating cancer, they could also involve risks.



Interventional radiology and intensity-modulated radiotherapy technology

Interventional fluoroscopy (IF) is a minimally invasive procedure that uses ionizing radiation in imaging guidance for diagnostic or treatment purposes. Although IF provides tremendous advantages over surgery, it must be implemented with care. Because many procedures are relatively new, the health risk of exposure to patients and physicians is not fully understood. To address this information gap, REB produced a brochure in collaboration with the Society of Interventional Radiology titled *Interventional Fluoroscopy: Reducing Radiation Risks for Patients and Staff.*

A cohort of 200,000 children and adolescents who received CT scans during a 10-year period will be followed for cancer incidence and mortality.

Kwangpyo Kim, Ph.D., a REB dosimetrist, recently completed a literature review assessing the radiation doses received by cardiologists who perform fluoroscopy-guided cardiac catheterizations. Additional reviews of exposure for other physicians using IF are under way. Moreover, within the field of pediatric interventional neuroradiology, which uses a noninvasive approach to treat vascular diseases of the central nervous system, REB dosimetrists estimated how much radiation is absorbed by the brain and assessed the individual lifetime risks of developing brain cancer among children who are treated in this manner. Branch researchers are also exploring the feasibility of conducting a study of cancer deaths among physicians who perform IF procedures.

The computed tomography (CT) scan, which creates a series of detailed pictures of areas inside the body taken from different angles to create cross-sectional views, is another widely used tool. Although valuable, growing use of CT scans has become a public health concern, particularly due to increased use among children. Epidemiological studies have shown that children are more sensitive to radiation than adults, and because children have longer life expectancies, there is a longer period for developing radiation damage.

Due to a lack of data on pediatric CT scan use and cancer, REB researchers initiated a retrospective study, in collaboration with epidemiologists at the University of Newcastle upon Tyne in the United Kingdom, to determine whether children undergoing this procedure are at increased risk. A cohort of 200,000 children and adolescents who received CT scans during a 10-year period will be followed for cancer incidence and mortality. Branch members are exploring the possibility of working with other institutions on an international, pooled analysis of cancer risk following pediatric CT scans.

Researchers in REB are also looking to the future by exploring options to evaluate the risk of secondary cancers due to intensity-modulated radiotherapy, a procedure that delivers radiation in varying intensities to a small area of tissue. Proton-beam radiotherapy, another new cancer treatment that delivers a radiation dose directly to tumor tissue, may be explored as well. The use of these technologies is expected to increase, so it is critical to evaluate the associated risks in coming years. ■

—Amber K. Boehm, Ph.D.

CONSORTIUM ADVANCES CHILDHOOD CANCER ETIOLOGIC RESEARCH

The second meeting of the International Childhood Cancer Cohort Consortium was held at the World Health Organization facility in Copenhagen in August. **Martha S. Linet, M.D., M.P.H.,** Chief of the Radiation Epidemiology Branch, and other members of the Consortium Steering Committee organized the event, which was sponsored by DCEG, the Division of Cancer Control and Population Sciences; the NIH Office of Rare Diseases; the National Children's Study; the U.S. Environmental Protection Agency; the Murdoch Children's Research Institute of Melbourne, Australia; and the Statens Serum Institute of Copenhagen, Denmark.

International Childhood Cancer Cohort Consortium meeting participants

Cohorts from around the world who sent representatives included: the Avon Longitudinal Study of Parents and Children (Dr. Jean Golding, University of Bristol, United Kingdom), Bradford Babies: Growing Up in Bradford (Dr. Patricia McKinney, University of Leeds, United Kingdom), the China-U.S. Collaborative Project on Birth Defects and Disabilities Prevention (Dr. Li Zhu, Peking University Health Sciences Center, Beijing, China), the China Family and Children Cohort Study (Dr. Zhu), the Danish National Birth Cohort (Dr. Jorn Olson, Copenhagen, Denmark), Étude Longitudinale Française depuis l'Enfance (Dr. Jacqueline Clavel, INSERM, Paris, France), the U.S. National Children's Study (Dr. Peter Scheidt, National Institute of Child Health and Human Development), the Norwegian Mother and Child Cohort Study (Dr. Andrei Grjibovski, Norwegian Institute of Public Health, Oslo, Norway), and the Tasmanian Infant Health Survey (Dr. Terry Dwyer, Murdoch Children's Research Institute).

Thirty-seven international investigators attended the meeting, including **Sharon A. Savage, M.D.** (Clinical Genetics Branch), and **Robert J. Biggar, M.D.** (Viral Epidemiology Branch).

Following an introduction and update on the consortium's progress, Dr. Linet provided an overview of international variation in childhood cancer incidence, known and postulated risk factors, and potential contributions of the cohort consortium. She indicated that the consortium is uniquely positioned to address etiologic hypotheses that are difficult to investigate in case-control studies, to identify precursor conditions, and to assess these conditions' transformation into malignancies. Presenters discussed key hypotheses about the roles of chromosomal translocations and hyperdiploidy at birth, parental age, pesticides, early infections, birth weight for gestational age, and birth defects in the etiology of childhood cancer.

On the second day, one breakout session discussed potential genetic and molecular studies, including those examining the role of copy number variation, global and gene-specific methylation, links to nutritional factors, and epimutation. Also discussed were sample collection and laboratory methods currently performed in large clinical laboratories, such as cord blood banking and translocation screening. The breakout group directed these technical discussions toward a large, multicenter, multi-cohort investigation. A second group discussed study design; data analysis; and administrative tools, such as core study protocols, data dictionaries, policies and procedures manuals, and membership guidelines, as well as ideas about how to credit authors.

Finally, the consortium established several working groups. One group will conduct a combined analysis on folate consumption and folic acid pathways in childhood leukemia and will prioritize other important hypotheses about the origins of childhood cancer. Another group of molecular epidemiologists and laboratory scientists will develop the methods for a pilot investigation that compares chromosomal translocations and hyperdiploidy at birth among different populations. This group will evaluate and prioritize genetic and molecular studies and develop and test approaches for biological sample collection, shipping, and storage. Other working groups will focus on approaches to the assessment and validation of pediatric cancer outcomes across the various cohorts and will finalize the consortium policies and procedures manual, including its institutional review board requirements and ethical and privacy concerns. ■

—Martha S. Linet, M.D., M.P.H.

YOUNG EPIDEMIOLOGY SCHOLARS COMPETITION

Elizabeth Zhao Lan and Casey Jao, high school students who worked as summer fellows in DCEG, were selected as regional finalists in the Fourth Annual Young Epidemiology Scholars (YES) competition. As one of the nation's most prestigious and influential events in high school science, the YES competition is designed to spur students' interest in the field of public health, especially epidemiology. Ms. Lan and Mr. Jao were selected from more than 800 entrants and each received a $2,000 scholarship. The 60 regional finalists were invited to present their work at a three-day event in Washington, DC in April.

Ms. Lan worked on a project titled "Genetic variation in catechol-*O*-methyltransferase *(COMT)* and obesity in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial," which was published in *Human Genetics.* The study, carried out under the mentorship of **Sophia S. Wang, Ph.D.,** Hormonal and Reproductive Epidemiology Branch (HREB), **Neil E. Caporaso, M.D.,** Genetic Epidemiology Branch, **Richard B. Hayes, D.D.S., Ph.D.,** Occupational and Environmental Epidemiology Branch, and **Lindsay M. Morton, Ph.D.** (HREB), found that COMT might be an important molecular target for the development of effective obesity treatments.

When asked what she learned from her research experience, Ms. Lan replied, "It has been found that obesity is the result of the interactions between heredity and the environment, not just genes alone. People may be more motivated to overcome their obesity if they know there is something they can do to reduce their weight. Targeted strategies could be developed for people with a *COMT* gene variant to combat weight gain."

Mr. Jao presented his project on "Developing statistical models to predict liver fibrosis in HCV-monoinfected and HCV/HIV-coinfected hemophiliacs," based on work with his primary mentor, **James J. Goedert, M.D.,** Chief of the Viral Epidemiology Branch (VEB).

Mr. Jao became interested in cirrhosis, a major cause of death among people with hemophilia who are infected with both hepatitis C virus (HCV) and human immunodeficiency virus (HIV), and especially in the possibility that anti-HIV medications might increase liver fibrosis. "Trying to figure out how to take care of these patients is difficult, especially because liver biopsies have been considered dangerous for hemophiliacs," Mr. Jao commented. He worked closely with Dr. David E. Kleiner of the Center for Cancer Research Laboratory of Pathology to understand liver pathology and with **Philip S. Rosenberg, Ph.D.,** Biostatistics Branch, to learn ordinal logistic regression modeling. In a prospective hemophilia cohort, Mr. Jao found that liver fibrosis increased among subjects who had a low platelet count. He concluded, "I'm glad that liver fibrosis wasn't higher with using anti-HIV medication, because those agents really save people's lives."

Ms. Lan has worked as a summer fellow in HREB for the past three summers. She graduated from Winston Churchill High School in Potomac, Maryland, and is now attending Columbia University. Mr. Jao has worked in VEB since 2005 while a student in the Math, Science, and Technology Research Program at River Hill High School in Clarksville, Maryland, and is now attending the California Institute of Technology.

The YES competition is sponsored by the Robert Wood Johnson Foundation and administered by the College Board. More information is available at www.collegeboard.com/yes/index.html. ■

—Kristin Kiser, M.H.A.

HOOVER GIVES NIH GORDON AWARD LECTURE

In May, **Robert N. Hoover, M.D., Sc.D.,** Director of the Epidemiology and Biostatistics Program, gave the Gordon Award Lecture as part of the NIH Director's Wednesday Afternoon Lecture Series. This honor, named for Robert S. Gordon, Jr., M.D., the first director of the NIH Office of Disease Prevention, is bestowed annually on a scientist who has contributed significantly to research in epidemiology or clinical trials.

NIH Director Elias Zerhouni presents the Gordon Award to Robert Hoover. *(Photograph Credit: Bill Branson)*

In his talk, titled "Hormones and breast cancer: Etiology vs. ideology," Dr. Hoover described how the last two decades of epidemiologic research helped clinicians and researchers to understand the role of hormones in breast cancer etiology and to move the field from "ideology" to evidence-based measures of risk and prevention. In the spirit of Dr. Gordon, Dr. Hoover stated, "Hard data are always superior to soft hypotheses," noting that despite the continued focus on estrogen as the main hormonal risk factor for breast cancer, researchers must remember to let the findings of large-scale population studies and clinical trials guide the field and inform new avenues of research.

—Alyssa Minutillo, M.P.H.

EVGENIA OSTROUMOVA STUDIES A UNIQUE EXPOSURE TO RADIOACTIVITY

When **Evgenia Ostroumova, M.D., Ph.D.,** joined the Radiation Epidemiology Branch (REB) as a post-doctoral fellow in 2006, she had just arrived in the United States from the Urals Research Center for Radiation Medicine (URCRM) in Chelyabinsk, Russia. At URCRM, she studied health effects of protracted exposure to ionizing radiation among the residents of the Techa River region in Russia.

In the late 1940s, the Mayak Production Association was established in the Southern Urals to produce weapons-grade plutonium and process fission materials. Due to the steady increase in plutonium production at the Mayak facility and a lack of reliable waste management and storage technology, sewage water containing radioactive materials was released into the nearby Techa River between 1949 and 1956. This practice resulted in considerable contamination of the river system and overexposure of residents in the Techa riverside villages. Approximately 30,000 residents of 41 rural villages were exposed to varying levels of a complex mixture of radionuclides, especially long-lived cesium-137 and strontium-90. Between 1953 and 1961, 7,000 people resettled from the contaminated areas to nearby villages.

In the 1960s, URCRM scientists began to collect information on persons exposed to the radiation to study the long-term health consequences of this exposure. During the following decade, they established a fixed cohort of males and females of all ages who lived in the Techa River villages during the period of significant radioactive contamination. Epidemiological studies of this cohort evolved over time, and the cohort expanded to include a low-dose group of people who moved to the villages when exposure was minimal. As a result of more than four decades of research and 50 years of follow-up, researchers have collected a wealth of information on the health status of this cohort. Dr. Ostroumova recalled that "the study of cancer risks in the Techa River cohort became an international collaboration in 1992, which enhanced the scientific approach and raised the quality of the epidemiological research program." She acknowledged the timeliness of her entry into the project in 1994.

Evgenia Ostroumova

While at NCI, Dr. Ostroumova collaborates on the project with her primary mentor, **Elaine Ron, Ph.D., M.P.H.** (REB), and Dr. Dale Preston from Hirosoft International Corporation. Currently, they are analyzing the cancer incidence and mortality of residents in the Techa River region. To date, they have found a significantly increased risk of leukemia and solid cancers in this population. Approximately 60% of the leukemia deaths, excluding chronic lymphoid leukemia, and 3% of all solid cancer deaths can be attributed to radiation exposure. Further, Dr. Ostroumova and her URCRM colleagues, in collaboration with researchers from Institut de Radioprotection et de Sûreté Nucléaire in France, conducted a nested case-control study of leukemia and demonstrated

Location of the Mayak Nuclear Facility

a radiation-related risk of non-chronic lymphoid leukemia, taking into account potential effect modifiers, such as sex, ethnicity, age at exposure, and history of any tumor prior to leukemia. Dr. Ostroumova and her colleagues also analyzed the risk of developing breast, lung, and stomach cancers after low-dose–rate radiation exposure.

Dr. Ostroumova has a particular interest in assessing the health effects of individuals exposed *in utero* and during early childhood. Several thousand members of the Techa River cohort had such exposures and are now reaching the age when evaluation of the radiation risk of adult-onset cancers can begin.

"I was in medical school when I became involved in this work," said Dr. Ostroumova, who received her M.D. from Chelyabinsk Medical Institute, Russia. "I performed field work initially and became very interested in radiation research." During her time at URCRM, Dr. Ostroumova received her Ph.D. in internal medicine from Russia's Tyumen Medical Academy. "It is difficult to combine an interest in this type of research and clinical medicine, so I had to make a choice," she said, and quickly added, "It was not a particularly difficult decision to make. I have no regrets."

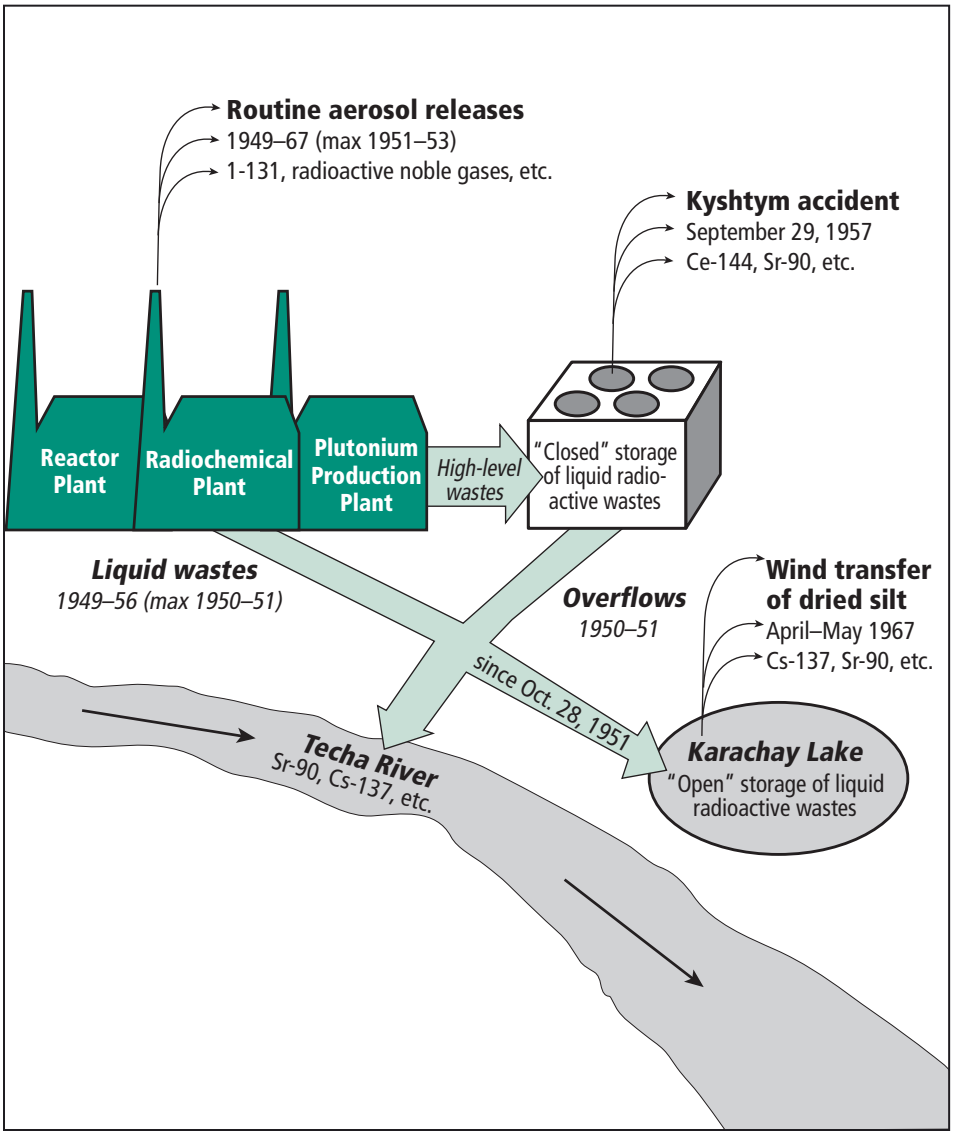
Although Dr. Ostroumova plans to stay at DCEG for one more year, she remains updated on the Techa River cohort through colleagues at URCRM.

Dr. Ostroumova contributes to other projects, including studies linking hypothyroidism to childhood radiation exposure from the Chornobyl accident and studies of cancer mortality among U.S. interventional fluoroscopists with an emphasis on brain tumors and leukemia. She also participates in non-radiation research, including an incidence survey of chronic lymphoid leukemia in the United States and worldwide.

Dr. Ostroumova has been very impressed by her experience at DCEG thus far. "When I told people where I was going, they indicated their respect for NCI as one of the premier cancer research centers in the world," she said. "The quality of the research here is exceptionally high, and it is very fast paced. I sometimes wonder if leaving NCI will feel like being on a high-speed train that comes to an abrupt stop." She noted the rigor applied to epidemiological analysis and manuscript writing and praised the high-quality mentorship provided by the Division.

Dr. Ostroumova believes that what she has learned at NCI will enrich the studies conducted at URCRM. Although the Techa River project remains a high priority, she is open about her future. "The opportunities afforded by working here are impressive," she said, "and I want to remain receptive to all of them." ■

—Amber K. Boehm, Ph.D.



A diagram of the Mayak Production Association and radioactive contamination of the environment

SUMMER FELLOWS INTRODUCED TO CANCER EPIDEMIOLOGY

DCEG Summer Fellows and Mentors: (front) Omobonike Oloruntoba, Leila Family, Rebecca Galbo, Erin Bardin Kent, Sanjeev Sreetharan, Cari Meinhold, and Cynthia Lin; (center) Erin Toops, Kristin Kiser, Joseph Fraumeni, Shelia Zahm, Demetrius Albanes, and Sheng-Chih Jin; (back) Susan Devesa, Jorge Toro, Candice Pfiester, Charles Rabkin, Jaime Bucher, Eric Engels, Amy Micheli, Mary Ward, Panta Rouhani, Philip Rosenberg, Kim Angelon, James Goedert, Annah Layman, Maureen Hatch, Veronica Wright, Sholom Wacholder, Blanche Alter, Aya Mitani, and Laura Sue.

Summer fellowships are an important way of introducing cancer epidemiology and genetics research to bright and energetic students. This summer, DCEG selected 24 students from 331 applicants to work at the Division, the largest number accepted to date. The group included three medical, four doctoral, six master's, seven undergraduate, and four high school students who were mentored by 26 DCEG researchers.

Students participated in research projects and presented their results at the Ninth Annual DCEG Summer Recognition and Poster Event. Organized by **Kristin Kiser, M.H.A.,** Fellowship Program Coordinator, and **Erin Toops,** Assistant Fellowship Coordinator,

Comments from 2007 Summer Fellows

"I felt that this summer really allowed me to be part of a research team of world-class scientists. Each staff member brought their expertise to the team and made our project come alive."

—Panta Rouhani, M.P.H.

"This summer internship has been an excellent chance for me to meet top researchers in the field and learn more about radiation epidemiology while gaining practical experience. I would highly recommend it to anyone interested in pursuing a career in epidemiology."

—Kim Angelon

"Working at DCEG has given me an opportunity to interact with scientists from such a wide variety of backgrounds, many of whom are experts in their respective fields, and all of whom have opened their doors to answer any questions I've had."

—Erin Bardin Kent

"I am very grateful for the opportunity to participate in the summer fellowship program. From conducting research with investigators at DCEG to attending lectures by professionals in the field of epidemiology to meeting other students who shared my passion for epidemiology, I feel more equipped to continue my education and prepare for a career in this field. In addition, I was able to use the research I conducted as a summer fellow to fulfill requirements for my master's program."

—Annah Layman

"The experiences I had in the short time at DCEG are invaluable. The staff has made me feel like a colleague, not at all like the inexperienced student I was when I arrived! I look forward to continuing the collaborations and contacts I've made."

—Amy Micheli

"I really, really enjoyed working this summer with another summer fellow, Candice Pfiester (Hood College) and my mentor **Maria Teresa Landi, M.D., Ph.D.** (Genetic Epidemiology Branch). Not only did I learn more than I expected about lung cancer, including its causes and current research activities, but I also learned that there are surprises; people I've met who commit to studying cancer are driven to improve peoples' lives. A career with such a selfless motivation really appeals to me. This internship exposed me to scientists I might not have otherwise encountered. It was wonderful to learn from and work with such knowledgeable, devoted investigators. The whole experience was a beautiful thing."

—Juliet Joly

DCEG Office of Education (OE), the event featured the work of 18 students who also presented their work at the NIH Summer Student Poster Session. The session concluded with a recognition ceremony and dialogue with **Joseph F. Fraumeni, Jr., M.D.,** DCEG Director, **Shelia Hoar Zahm, Sc.D.,** DCEG Deputy Director, and **Demetrius Albanes, M.D.,** Chief of OE and senior investigator in the Nutritional Epidemiology Branch (NEB).

Students interested in working at DCEG in 2008 can submit their online applications starting in November to the Division's summer fellowship web page (www.dceg.cancer.gov/fellowships/summerprogram). ■

—Kristin Kiser, M.H.A.

RESEARCH POSTERS AND PROJECTS BY THE 2007 SUMMER FELLOWS

- *Combinability of exposure groups to evaluate* in utero *effects of radiation.* **Kim Angelon,** University of North Carolina at Chapel Hill. Mentor: **Maureen C. Hatch, Ph.D.** (Radiation Epidemiology Branch [REB])

- *Predictors of water and total fluid consumption for adults in the United States.* **Elizabeth Atchison,** St. Olaf College. Mentors: **Gloria Gridley, M.S.,** and **Barry I. Graubard, Ph.D.** (Biostatistics Branch [BB])

- *Evaluating cancer risk from acrylamide in foods.* **Tara Baris,** McGill University. Mentor: **Rashmi Sinha, Ph.D.** (NEB)

- *Complementary and alternative medicine use among women at high risk of breast cancer.* **Jaime Bucher,** University of Toledo. Mentor: **Larissa A. Korde, M.D., M.P.H.** (Clinical Genetics Branch [CGB])

- *NCI Inherited Bone Marrow Failure Syndromes Study: Diagnoses, lab parameters, and DNA.* **Leila Family,** University of California, Los Angeles. Mentors: **Neelam Giri, M.D.,** and **Blanche P. Alter, M.D., M.P.H.** (CGB)

- *Statistical methods in genome-wide association studies.* **Sheng-Chih Jin,** Johns Hopkins University. Mentor: **Sholom Wacholder, Ph.D.** (BB)

- *Comparison of insecticide levels in carpet dust and self-reported pest treatment practices in the Northern California Childhood Leukemia Study.* **Erin Bardin Kent,** University of California, Irvine. Mentor: **Mary H. Ward, Ph.D.** (Occupational and Environmental Epidemiology Branch [OEEB])

- *Incidence of kidney and bladder cancers among people with AIDS in the United States.* **Annah Layman,** Brigham Young University. Mentor: **Eric A. Engels, M.D., M.P.H.** (Viral Epidemiology Branch [VEB])

- *Intestinal parasite infection and risk of Kaposi sarcoma in Uganda.* **Cynthia Lin,** University of Chicago. Mentors: **Charles S. Rabkin, M.D.,** and **Sam M. Mbulaiteye, M.D.** (VEB)

- *Predictors of fasting serum insulin and glucose and risk of pancreatic cancer in Finnish male smokers.* **Cari Meinhold,** Johns Hopkins University. Mentor: **Rachael Stolzenberg-Solomon, M.P.H., Ph.D.** (NEB)

- *An engineering approach to detecting periodicities in biomedical time series.* **Allison Meisner,** University of Connecticut. Mentor: **Philip S. Rosenberg, Ph.D.** (BB)

- *A pilot study to increase physical activity in sedentary women at high risk for breast cancer and breast cancer survivors: Recruitment and retention.* **Amy Micheli,** Thomas Jefferson University. Mentor: Dr. Korde

- *Racial differences in shifting U.S. Breast Cancer Trends (SEER; 1975–2004).* **Aya Mitani,** Yale University. Mentors: **Ruth M. Pfeiffer, Ph.D.,** and **William F. Anderson, M.D., M.P.H.** (BB)

- *Phenotypic spectrum of dyskeratosis congenita.* **Omobonike Oloruntoba,** University of Maryland, College Park. Mentor: **Sharon A. Savage, M.D.** (CGB)

- *Digital imaging in lung cancer diagnosis.* **Candice Pfiester,** Hood College, and **Juliet Joly,** University of Notre Dame. Mentor: **Maria Teresa Landi, M.D., Ph.D.** (Genetic Epidemiology Branch [GEB])

- *Cutaneous soft tissue sarcoma incidence patterns in the Surveillance, Epidemiology, and End Results Program, 1978–2004: An analysis of 12,114 cases.* **Panta Rouhani, M.P.H.,** University of Miami. Mentor: **Jorge R. Toro, M.D.** (GEB)

- *If Hardy is affected, is Weinberg too? Elevated genetic risk in siblings from common low-penetrance variants.* **Sanjeev Sreetharan,** Walt Whitman High School. Mentor: Dr. Wacholder

- *Energy balance and risk of postmenopausal breast cancer in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.* **Laura Sue,** Yale University. Mentor: **Regina G. Ziegler, Ph.D., M.P.H.** (Epidemiology and Biostatistics Program)

- *The prevalence of autoimmune diseases in the elderly American population.* **Veronica Wright,** Southern Illinois University, Carbondale. Mentors: **James J. Goedert, M.D.,** and **Shahinaz Gadalla, M.D., M.S.** (VEB)

- *Evaluating statistical packages for genome-wide association studies.* **Nicolae Melita,** Polytechnic University, Timisoara, Romania. Mentors: Dr. Wacholder and **Kai Yu, Ph.D.** (BB)

WORKSHOP AIMS TO FURTHER RESEARCH ON RARE CANCERS

In May, a workshop on "Synergizing epidemiologic research on rare cancers" was held in Bethesda. Cosponsored by the Division of Cancer Control and Population Sciences (DCCPS) and the NIH Office of Rare Diseases, the workshop focused on stimulating research in understudied or rare cancers, which were defined as cancers with incidence rates of less than 15 cases per 100,000 population or fewer than 40,000 new cases per year in the United States. The workshop placed particular emphasis on furthering research in multiple myeloma, esophageal and liver cancers, and sarcomas. Efforts were made to identify opportunities and resources for epidemiologic research on rare cancers, create collaborations to enhance the size and efficiency of studies of rare cancers, and determine the best means of expanding consortia.

Workshop Participants: Shannon Lemrow (DCCPS), Sholom Wacholder, and Sara Strom (M.D. Anderson Cancer Center). *(Photograph Credit: Keith Richardson)*

Several DCEG investigators participated in the workshop. **Patricia Hartge, Sc.D.,** Deputy Director of the Epidemiology and Biostatistics Program (EBP), and **Shelia Hoar Zahm, Sc.D.,** Deputy Director of DCEG, were members of the steering committee. **Dalsu Baris, M.D., Ph.D.,** of the Occupational and Environmental Epidemiology Branch (OEEB), chaired the multiple myeloma working group; **Wong-Ho Chow, Ph.D.** (OEEB), chaired the esophageal cancer working group; **Katherine McGlynn, Ph.D.,** of the Hormonal and Reproductive Epidemiology Branch, chaired the liver cancer working group; and **Sharon A. Savage, M.D.,** of the Clinical Genetics Branch, chaired the sarcoma working group. Dr. Hartge gave a talk titled "Cohort consortia and epidemiologic research on rare cancers"; **Robert N. Hoover, M.D., Sc.D.,** Director of EBP, spoke on "Genome-wide association studies in rare cancers"; **Nathaniel Rothman, M.D.** (OEEB), spoke about "Urinary bladder cancer consortium: Pre-consortium challenges"; and **Sholom Wacholder, Ph.D.,** Biostatistics Branch, cochaired the methods and strategies working group and spoke on "Selection of controls in studies of rare cancers."

At the conclusion of the workshop, recommendations were made on ways to: 1) encourage the development of mechanisms to support and facilitate data sharing, such as central data management or coordinating centers; 2) standardize exposure collection questionnaires; 3) develop strategies to encourage young investigators toward rare cancer research; 4) develop improved web-based tools to pool existing data; 5) conduct symposia about methods for research on rare cancers at national cancer meetings; and 6) foster greater collaboration between investigators, community or advocacy groups, and relevant foundations to improve enrollment in studies. ■

—Katherine McGlynn, Ph.D.

BIOLOGICAL AND ENVIRONMENTAL REPOSITORIES MEETING

From May 30 to June 3, **Marianne Henderson, M.S.,** Chief of the Office of Division Operations and Analysis, **Karen E. Pitt, Ph.D.,** of the Office of the Director (OD), and **Jim B. Vaught, Ph.D.** (OD), participated in the annual meeting of the International Society for Biological and Environmental Repositories in Singapore. The focus for this year was scientific and regulatory aspects of collecting, processing, and storing biological specimens for research and clinical applications around the globe. Dr. Vaught gave two presentations, the first during a plenary session on "NCI's efforts towards evidence-based standards: The biospecimen research network" and the second as part of a panel discussion on "Economic analysis, evaluation, and funding." Dr. Pitt spoke on the "Considerations in the development and implementation of sample culling policies and practices" and chaired a panel discussion on "The design and implementation of quality management systems for specimen collections." Ms. Henderson reviewed the "Economics and financial management of a large biomedical repository program."

SCIENTIFIC HIGHLIGHTS

BREAST CANCER

Hormone Therapy, Mammography, and Estrogen Receptor Status

Using data from Kaiser Permanente Northwest, a prepaid U.S. health plan, age-specific and age-adjusted breast cancer incidence rates (two-year moving averages) were compared with use of screening mammography and dispensed menopausal hormone therapy (MHT) prescriptions between 1980 and 2006, during which time 7,386 incident invasive breast cancers were diagnosed among plan members. Breast cancer incidence rates per 100,000 women rose 25% from a rate of 105.6 during the early 1980s to 131.7 during 1992 and 1993, then rose by an additional 15% to 151.3 through 2000 and 2001. The rate then dropped by 18% to 123.6 for years 2003 and 2004 and rose slightly to 126.2 in 2005 and 2006 (see Figure 1). This pattern was largely restricted to women aged 45 years or older and to estrogen receptor–positive (ER+) breast cancers. Rates of mammography screening sharply increased from 1980 to 1993 but then leveled off. MHT dispensing, particularly of estrogen-plus-progestin formulations, increased from 1988 to 2002 but then dropped about 75% after 2002. The authors concluded that recent trends in breast cancer incidence rates, particularly for ER+ tumors, parallel major changes in patterns of mammography screening and MHT use. **(Glass AG, Lacey JV Jr, Carreon JD, Hoover RN. Breast cancer incidence, 1980–2006: Combined roles of menopausal hormone therapy, screening mammography, and estrogen receptor status. *J Natl Cancer Inst* 2007;99:1152–1161)**

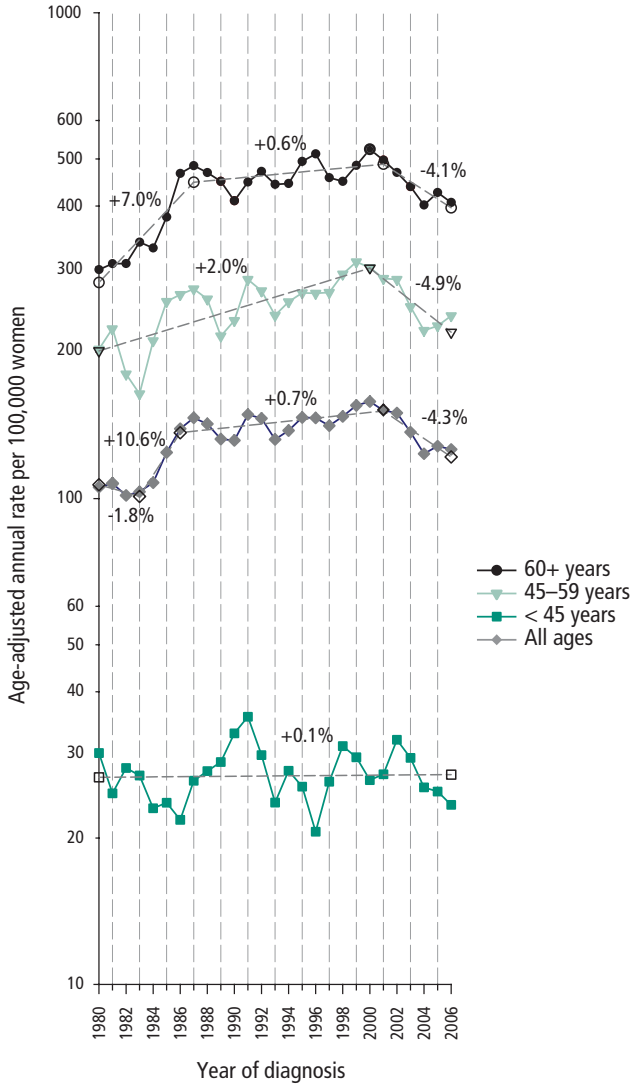


Figure 1. Age-adjusted annual incidence rates for invasive breast cancer at Kaiser Permanente Northwest (KPNW), 1980–2006, for all ages and age groups. **Data points** reflect two-year moving averages based on the KPNW tumor registry and KPNW administrative files of female health plan members, with the individual-year data reflecting the two-year moving average of that year plus the previous year. Joinpoint regression and annual percentage changes in incidence are superimposed on incidence plots. **Open symbols** represent statistically significant changes in incidence (i.e., joinpoints) based on joinpoint regression; dashed lines represent straight-line segments between joinpoints. Adjacent numbers represent annual percentage changes for those segments. (Glass AG, et al. 2007)

Risk Factors for Molecular Subtypes

This study evaluated whether pathologic features and etiologic associations differ by molecular subtype of breast cancer among 804 women with invasive breast cancers and 2,502 controls from the Polish Breast Cancer Study. Immunohistochemical stains for estrogen receptor alpha, progesterone receptor, human epidermal growth factor receptors (HER2 and HER1), and cytokeratin 5 were used to classify cases into five molecular subtypes: luminal A, luminal B, HER2-expressing, basal-like, and unclassified. Compared with the predominant luminal A tumors (69%), other subtypes were associated with unfavorable clinical features at diagnosis, especially HER2-expressing (8%) and basal-like (12%) tumors. Increasing

body mass index (BMI) significantly reduced the risk of luminal A tumors among premenopausal women but did not reduce risk for basal-like tumors. Reduced risk associated with increasing age at menarche was stronger for basal-like than for luminal A tumors. Although family history increased risk for all subtypes (except for unclassified tumors), the magnitude of the relative risk (RR) was highest for basal-like tumors. Breast cancer risk factors could vary by molecular subtypes, suggesting etiologic, in addition to clinical, heterogeneity of breast cancer. **(Yang XR, Sherman ME, Rimm DL, Lissowska J, Brinton LA, Peplonska B, Hewitt SM, Anderson WF, Szeszenia-Dabrowska N, Bardin-Mikolajczak A, Zatonski W, Cartun R, Mandich D, Rymkiewicz G, Ligaj M, Lukaszek S, Kordek R, García-Closas M. Differences in risk factors for breast cancer molecular subtypes in a population-based study. *Cancer Epidemiol Biomarkers Prev* 2007;16:439–443)**

CERVICAL CANCER

Seminar on Human Papillomavirus and Cervical Cancer

Cervical cancer is the second most common cancer in women worldwide, and knowledge about its cause and pathogenesis is expanding rapidly. Persistent infection with 1 of about 15 genotypes of carcinogenic human papillomavirus (HPV) causes almost all cases of cervical cancer. There are four major steps in cancer development: infection of metaplastic epithelium at the cervical transformation zone, viral persistence, progression of persistently infected epithelium to cervical precancer, and invasion through the basement membrane of the epithelium. Infection is extremely common in young women in their first decade of sexual activity. Persistent infections and precancer are established, typically within 5 to 10 years, from less than 10% of new infections. Invasive cancer arises over many years, even decades, in a minority of women with precancer, with peak or plateau in risk between about 35 and 55 years of age. Each genotype of HPV acts as an independent infection, with differing carcinogenic risks linked to evolutionary species. The authors suggest that understanding the steps in cervical cancer pathogenesis can guide prevention and control, and that if applied wisely, HPV-related technology can minimize the incidence of cervical cancer and the morbidity and mortality it causes, even in low-resource settings. **(Schiffman M, Castle PE, Jeronimo J, Rodriguez AC, Wacholder S. Human papillomavirus and cervical cancer. *Lancet* 2007;370:890–907)**

DIETHYLSTILBESTROL

Prenatal Exposure

Total and site-specific cancer risks were evaluated among women prenatally exposed to diethylstilbestrol (DES). There was no overall excess risk in exposed women when compared with external rates (standardized incidence ratio [SIR] = 1.01; CI = 0.86–1.2); however, the overall RR comparing exposed with unexposed women was 1.32 (CI = 0.94–1.8). Breast cancer risk was elevated only among women aged more than 40 years (RR = 1.83; CI = 1.1–3.2). The clear cell adenocarcinoma (CCA) SIR among exposed women was nearly 40, and the estimated attack rate through age 39 was 1.6 per 1,000 women. CCA incidence was more than 80% lower after age 25 than from ages 20 to 24. Excluding CCA and breast cancer, the overall RR was 1.21 (CI = 0.74–2.0). DES exposure was not associated with excess risk of endometrial or ovarian cancer. Results suggest that the DES-associated increase in CCA incidence remains elevated through the reproductive years. Because the population is still young, continued follow-up is necessary to assess the carcinogenic impact of prenatal DES exposure. **(Troisi R, Hatch EE, Titus-Ernstoff L, Hyer M, Palmer JR, Robboy SJ, Strohsnitter WC, Kaufman R, Herbst AL, Hoover RN. Cancer risk in women prenatally exposed to diethylstilbestrol. *Int J Cancer* 2007;121:356–360)**

ENDOMETRIAL CANCER

Hormone Therapy

Endometrial cancer risks associated with the use of sequential and continuous estrogen-plus-progestin regimens were assessed in the NIH-AARP Diet and Health Study, including 73,211 women aged 50 to 71 years at baseline. Linkage to state cancer registries and mortality indices identified 433 incident endometrial cancers. Among 51,312 women who never used hormones or only used estrogen-plus-progestin regimens at doses consistent with current practice, neither sequential estrogen-plus-progestin (daily estrogen-plus-progestin for 10–14 days per cycle: RR = 0.74; CI = 0.39–1.40) nor continuous estrogen-plus-progestin (use for ≥ 20 days per cycle: RR = 0.80; CI = 0.55–1.15) had any statistically significant association with endometrial cancer. Long durations (five years or more) of sequential regimen use (RR = 0.79; CI = 0.38–1.66) and of continuous regimen use (RR = 0.85; CI = 0.53–1.36) also were not associated with endometrial cancer risk. **(Lacey JV Jr, Leitzmann MF, Chang SC, Mouw T, Hollenbeck AR, Schatzkin A, Brinton LA. Endometrial cancer and menopausal hormone therapy in the National Institutes of Health-AARP Diet and Health Study cohort. *Cancer* 2007;109:1303–1311)**

ESOPHAGEAL AND GASTRIC CANCERS

Helicobacter pylori

In a cohort of 29,584 residents of Linxian, China, followed from 1985 to 2001, a case-cohort study of the association of *H. pylori* seropositivity with cancer risk was conducted in a random sample of 300 esophageal squamous cell carcinoma (ESCC) and 600 gastric

cardia adenocarcinomas, all 363 diagnosed gastric noncardia adenocarcinomas, and a random sample of the entire cohort (n = 1,050). Baseline serum was evaluated for IgG antibodies to whole-cell and CagA *H. pylori* antigens by enzyme-linked immunosorbent assay. Risks of both gastric cardia (hazard ratio [HR] = 1.64; CI = 1.26–2.14) and noncardia (HR = 1.60; CI = 1.15–2.21) cancers increased in individuals exposed to *H. pylori*, whereas risk of esophageal squamous cell cancer was not affected (HR = 1.17; CI = 0.88–1.57). HRs for both cardia and noncardia cancers were higher in younger individuals. With longer time between serum collection and cancer diagnosis, associations became stronger for cardia cancers but weaker for noncardia cancers. **(Kamangar F, Qiao YL, Blaser MJ, Sun XD, Katki H, Fan JH, Perez-Perez GI, Abnet CC, Zhao P, Mark SD, Taylor PR, Dawsey SM. *Helicobacter pylori* and esophageal and gastric cancers in a prospective study in China. *Br J Cancer* 2007;96:172–176)**

Tobacco and Alcohol

The authors investigated the associations of alcohol and tobacco with esophageal and gastric cancer risks in 474,606 U.S. participants in the NIH-AARP Diet and Health Study. Between 1995 and 2000, 97 incident cases of ESCC and 205 of esophageal, 188 of gastric cardia, and 187 of gastric noncardia adenocarcinoma occurred. Compared with nonsmokers, current smokers were at increased risk for ESCC (HR = 9.27; CI = 4.04–21.29) and esophageal (HR = 3.70; CI = 2.20–6.22), gastric cardia (HR = 2.86; CI = 1.73–4.70), and gastric noncardia (HR = 2.04; CI = 1.32–3.16) adenocarcinoma. Assuming causality, ever smoking had population attributable risks of 77% (CI = 0.55–0.89) for ESCC and 58% (CI = 0.38–0.72) for esophageal, 47% (CI = 0.27–0.63) for gastric cardia, and 19% (CI = 0.00–0.37) for gastric noncardia adenocarcinoma. For drinkers of more than three alcoholic beverages per day, compared with those whose intake was up to one drink per day, a significant association was found between alcohol intake and ESCC risk (HR = 4.93; CI = 2.69–9.03) but not esophageal, gastric cardia, or gastric noncardia adenocarcinoma risk. **(Freedman ND, Abnet CC, Leitzmann MF, Mouw T, Subar AF, Hollenbeck AR, Schatzkin A. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. *Am J Epidemiol* 2007;165:1424–1433)**

LUNG CANCER

Gene Variants in Inflammation Pathway

A panel of 59 SNPs in 37 inflammation-related genes was evaluated among non-Hispanic white lung cancer cases (n = 1,553) and controls (n = 1,730) from Houston, Texas. Interleukin 1 beta (*IL1B*) C3954T was associated with lung cancer (OR = 1.27; CI = 1.10–1.47; false positive-report probability [FPRP] = 0.148). Two *IL1A* SNPs (C-889T and $Ala^{114}Ser$) were also related to lung cancer (OR = 1.18–1.22), although FPRPs were higher. One *IL1A-IL1B* haplotype, containing only the *IL1B* 3954T allele, was associated with elevated lung cancer risk (OR = 1.80; CI = 1.24–2.61). These associations were stronger in heavy smokers, particularly for *IL1B* C3954T (OR = 1.59; CI = 1.28–1.97; FPRP = 0.004). Lung cancer risk was unrelated to polymorphisms in IL1 receptor or antagonist genes. Associations with lung cancer were also seen for SNPs in granulocyte-macrophage colony-stimulating factor and peroxisome proliferator-activated factor-delta, but FPRPs were high. A dysregulated inflammatory response to tobacco-induced lung damage might promote carcinogenesis. **(Engels EA, Wu X, Gu J, Dong Q, Liu J, Spitz MR. Systematic evaluation of genetic variants in the inflammation pathway and risk of lung cancer. *Cancer Res* 2007;67:6520–6527)**

LYMPHOMA

Caspase Gene Variants and Non-Hodgkin Lymphoma

Five single nucleotide polymorphisms (SNPs) in four key caspase genes, *CASP3* (Ex8-280C→A [rs6948] and Ex8+567T→C [rs1049216]), *CASP8* Ex14-271A→T (rs13113), *CASP9* Ex5+32G→A (rs1052576), and *CASP10* Ex3-171A→G (rs3900115), were studied in relation to non-Hodgkin lymphoma (NHL) risk in a population-based case-control study of women in Connecticut (461 cases and 535 controls). Variants in *CASP3* and *CASP9* were significantly associated with decreased risk for NHL, particularly follicular lymphoma. Further, variants in *CASP3*, *CASP8*, and *CASP10* were associated with a decreased risk of marginal zone lymphoma, and variants in *CASP3* and *CASP10* were associated with a lower risk of chronic lymphocytic leukemia and related subtypes. The striking protective associations observed for polymorphisms in all four genes for NHL and/or one or more subtypes suggest that genetic variation in *CASP* genes might play an important role in the etiology of NHL. **(Lan Q, Zheng T, Chanock S, Zhang Y, Shen M, Wang SS, Berndt SI, Zahm SH, Holford TR, Leaderer B, Yeager M, Welch R, Hosgood D, Boyle P, Rothman N. Genetic variants in caspase genes and susceptibility to non-Hodgkin lymphoma. *Carcinogenesis* 2007;28:823–827)**

Hepatitis C Virus Infection and NHL

To test the hypothesis that hepatitis C virus (HCV) infection is associated with increased risk for hematological malignancies, related lymphoproliferative disorders, and thyroid cancer, a retrospective cohort study of users of U.S. Veterans Affairs health care

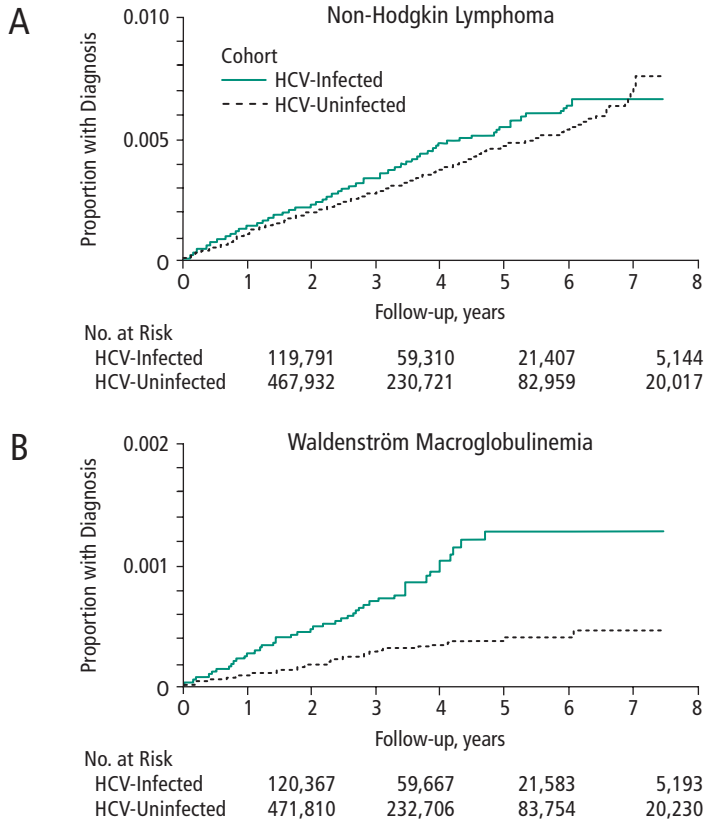


Figure 2. Kaplan-Meier estimates of the cumulative incidence of two outcomes among veterans infected and uninfected with HCV. (Giordano TP, et al. 2007)

facilities from 1997 to 2004 was conducted, including 146,394 patients infected with HCV and 572,293 uninfected patients. Risks for NHL (n = 1,359), Waldenström macroglobulinemia (n = 165), and cryoglobulinemia (n = 551) increased with HCV infection (adjusted HR = 1.28, CI = 1.12–1.45; HR = 2.76, CI = 2.01–3.79; and HR = 3.98, CI = 3.36–4.72, respectively) (see Figure 2). No significantly increased risks were found for other hematological malignancies. Although thyroiditis risk was slightly increased, risk for thyroid cancer (n = 320) was not (HR = 0.72; CI = 0.52–0.99). **(Giordano TP, Henderson L, Landgren O, Chiao EY, Kramer JR, El Serag H, Engels EA. Risk of non-Hodgkin lymphoma and lymphoproliferative precursor diseases in U.S. veterans with hepatitis C virus. *JAMA* 2007;297:2010–2017)**

High-density Lipoprotein Cholesterol and NHL

The relationship between prediagnostic high-density lipoprotein cholesterol (HDL-C) and NHL was investigated in the Alpha-tocopherol Beta-carotene Cancer Prevention Study cohort. At baseline, serum HDL-C and total cholesterol concentrations from fasting blood, information on diet and lifestyle, and direct measurements of height, weight, and blood pressure were obtained from 27,074 healthy male smokers aged 50 to 69 years. No association was found between total or non-HDL cholesterol in the 201 incident NHL cases ascertained during follow-up (1985–2002), but an inverse association between HDL-C and NHL that changed with length of follow-up was observed. High HDL-C was associated with lower risk of all NHL during the first 10 years but not with diagnoses during later follow-up. The inverse association was similar for NHL subtypes and was not modified by obesity, blood pressure, physical activity, or alcohol intake but seemed to be stronger in men with shorter durations of smoking. **(Lim U, Gayles T, Katki HA, Stolzenberg-Solomon R, Weinstein SJ, Pietinen P, Taylor PR, Virtamo J, Albanes D. Serum high-density lipoprotein cholesterol and risk of non-Hodgkin lymphoma. *Cancer Res* 2007;67:5569–5574)**

Immune Mechanisms and NHL

The joint effects of established NHL risk factors and tumor necrosis factor (*TNF*) G308A or interleukin 10 (*IL10*) T3575A genotypes were investigated. Among 1,172 cases and 982 population-based controls in a U.S. multicenter study, NHL risks increased among those with both an autoimmune condition and the *TNF* G308A GA/AA (OR = 2.1; CI = 1.0–4.2) or the *IL10* T3575A TA/AA (OR = 1.6; CI = 0.9–2.6) genotype compared with individuals without an autoimmune condition and with the common *TNF* G308A GG or *IL10* T3575A TT genotype, respectively; results were similar for diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma. Elevated DLBCL risk associated with last-born status was more pronounced among those with *TNF* G308A GA/AA (OR = 2.7; CI = 1.1–6.4) or *IL10* T3575A TA/AA (OR = 2.9; CI = 1.6–5.2) genotype. Similarly, elevated DLBCL risk associated with obesity (BMI ≥ 35 vs. < 25 kg/m^2) was observed only among those with *TNF* G308A GA/AA (OR = 2.5; CI = 1.1–5.7) or *IL10* T3575A TA/AA (OR = 2.0; CI = 1.1–3.5) genotype. Autoimmune conditions, late birth order, and obesity might act partly through a common inflammatory pathway, posing a greater risk to individuals with variant *TNF* and *IL10* genotypes than to those with wild-type alleles. **(Wang SS, Cozen W, Cerhan JR, Colt**

JS, Morton LM, Engels EA, Davis S, Severson RK, Rothman N, Chanock SJ, Hartge P. Immune mechanisms in non-Hodgkin lymphoma: Joint effects of the TNF G308A and IL10 T3575A polymorphisms with non-Hodgkin lymphoma risk factors. *Cancer Res* 2007;67:5042–5054)

Polychlorinated Biphenyls and NHL

The authors examined associations of specific polychlorinated biphenyl (PCB) congeners with NHL in three prospective cohorts. Using prediagnostic serum or plasma, they measured the concentrations of selected PCB congeners among NHL cases and controls from these cohorts: Janus (190 cases and 190 controls), CLUE I (74 cases and 147 controls), and the Nurses' Health Study (30 cases and 78 controls). Several congeners (i.e., 118, 138, and 153) that were present at higher levels and were moderately to highly correlated with each other showed exposure-response trends with risk of NHL in all three cohorts. These associations were observed primarily among subjects diagnosed closer to the date of blood collection in the two cohorts with sufficient cases to permit stratification by time. Among cases diagnosed before the median years of follow-up (16 years in Janus and 12 years in CLUE I), ORs and CIs for increasing quartiles of concentration of congener 118 relative to the lowest quartile were 2.4 (0.9–6.5), 4.9 (1.6–15.3), and 5.3 (1.5–18.8; p for trend < 0.005) in Janus and 8.1 (1.0–68.9), 6.6 (0.7–59.0), and 13.0 (1.6–106.8; p for trend < 0.05) in CLUE I. Similar patterns were seen for congeners 138 and 153 and for total PCBs. **(Engel LS, Laden F, Andersen A, Strickland PT, Blair A, Needham LL, Barr DB, Wolff MS, Helzlsouer K, Hunter DJ, Lan Q, Cantor KP, Comstock GW, Brock JW, Bush D, Hoover RN, Rothman N. Polychlorinated biphenyl levels in peripheral blood and non-Hodgkin's lymphoma: A report from three cohorts. *Cancer Res* 2007; 67:5545–5552)**

METHODS

Efficient Screening of SNP Associations

The authors investigated an analytic strategy for assessing associations between SNPs and binary disease outcomes in which the observed genotype frequencies of cases are compared with the expected genotype frequencies of controls assuming Hardy-Weinberg equilibrium (HWE). Closed-form expressions for maximum likelihood estimates of the genotype-specific disease OR parameters and related variance-covariances were derived. Based on these estimates and their variance-covariance structure, a two-degree-of-freedom test for disease-SNP association was proposed. The test can have substantially higher power than a variety of existing methods, especially when the true effect of the SNP is recessive. Analytic expressions for the bias of OR estimates when the underlying HWE assumption was violated were obtained. The authors concluded that the novel test would be particularly useful for analyzing data from the initial screening stages of contemporary multistage association studies. **(Chen JB, Chatterjee N. Exploiting Hardy-Weinberg equilibrium for efficient screening of single SNP associations from case-control studies. *Hum Hered* 2007;63:196–204)**

OSTEOSARCOMA

Growth Regulation Genes

Fifty-two common SNPs in 13 genes involved in growth regulation were genotyped in a prospective case-control study of osteosarcoma (104 osteosarcoma cases and 74 orthopedic controls). Genotype data analyzed with contingency tables suggested the strongest association with insulin-like growth factor 2 receptor (*IGF2R*) SNPs. *IGF2R* Ex16+88G→A (rs998075) and IVS16+15C→T (rs998074) SNPs were associated with increased risk for osteosarcoma compared with orthopedic controls (haplotype OR = 2.04; CI = 1.29–3.24). Follow-up genotyping showed that *IGF2R* IVS15+213C→T was also associated with increased osteosarcoma risk. Resequence analysis identified two additional SNPs linked to the risk-associated SNPs; linkage disequilibrium was strongest in a 1-kb pair region around them. The Ex16+88G→A SNP is located within a CpG island and alters methylation at that site. This pilot study of germline genetic variation in growth pathway genes and osteosarcoma identified a haplotype block in *IGF2R* associated with increased risk of osteosarcoma. The presence of a SNP in this block results in loss of methylation at a CpG island, providing evidence of a possible functional variant. **(Savage SA, Woodson K, Walk E, Modi W, Liao J, Douglass C, Hoover RN, Chanock SJ; National Osteosarcoma Etiology Study Group. Analysis of genes critical for growth regulation identifies insulin-like growth factor 2 receptor variations with possible functional significance as risk factors for osteosarcoma. *Cancer Epidemiol Biomarkers Prev* 2007;16:1667–1674)**

PROSTATE CANCER

Serum Carotenoids

The associations between prediagnostic serum carotenoids (lycopene, alpha-carotene, beta-carotene, beta-cryptoxanthin, lutein, and zeaxanthin) and risk of prostate cancer were investigated in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. The study included 692 incident prostate cancer cases, diagnosed one to eight years after entry, including 270 aggressive cases with regional or distant stage (n = 90) or Gleason score of at least 7 (n = 235) and 844 randomly selected, matched controls. No association was observed between serum lycopene and total prostate cancer (OR = 1.14; CI = 0.82–1.58 for highest vs. lowest quintile; p for trend = 0.28) or aggressive prostate cancer (OR = 0.99; CI = 0.62–1.57 for

highest vs. lowest quintile; *p* for trend = 0.43). Beta-carotene was associated with an increased risk of aggressive prostate cancer (OR = 1.67; CI = 1.03–2.72 for highest vs. lowest quintile; *p* for trend = 0.13), especially regional or distant stage disease (OR = 3.16; CI = 1.37–7.31 for highest vs. lowest quintile; *p* for trend = 0.02); other carotenoids were not associated with risk. **(Peters U, Leitzmann MF, Chatterjee N, Wang Y, Albanes D, Gelmann EP, Friesen MD, Riboli E, Hayes RB. Serum lycopene, other carotenoids, and prostate cancer risk: A nested case-control study in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. *Cancer Epidemiol Biomarkers Prev* 2007;16:962–968)**

Multivitamin Use

The association between multivitamin use and risk of prostate cancer was investigated among 295,344 men enrolled in the NIH-AARP Diet and Health Study. During five years of follow-up, 10,241 participants were diagnosed with incident prostate cancer, including 8,765 localized and 1,476 advanced cancers. In a separate mortality analysis with six years of follow-up, 179 cases of fatal prostate cancer were ascertained. No association was observed between multivitamin use and risk of localized prostate cancer. However, an increased risk of advanced (RR = 1.32; CI = 1.04–1.67) and fatal (RR = 1.98; CI = 1.07–3.66) prostate cancers among men who reported excessive use of multivitamins (more than seven times per week) was found when compared with those who never used multivitamins. The incidence rates per 100,000 person-years for advanced and fatal prostate cancers for those with excessive multivitamin use were 143.8 and 18.9, respectively, compared with 113.4 and 11.4 in non-users. The positive associations with excessive multivitamin use were strongest in men with a family history of prostate cancer or who took individual micronutrient supplements, including selenium, beta-carotene, or zinc. **(Lawson KA, Wright ME, Subar A, Mouw T, Hollenbeck A, Schatzkin A, Leitzmann MF. Multivitamin use and risk of prostate cancer in the National Institutes of Health-AARP Diet and Health Study. *J Natl Cancer Inst* 2007;99:754–764)**

TESTICULAR CANCER

Relationship to Height

To clarify the relationships of body size, age at puberty, and dairy product consumption with testicular germ cell tumor (TGCT) risk, the authors analyzed data from 767 cases and 928 controls in the Servicemen's Testicular Tumor Environmental and Endocrine Determinants Study. Increased height was significantly related to risk (OR = 1.83; CI = 1.36–2.45), whereas BMI was not (OR = 1.06; CI = 0.66–1.69). There was no association with age at puberty, based on ages at first shaving (OR = 1.29; CI = 0.96–1.73), voice changing (OR = 0.97; CI = 0.71–1.32), and nocturnal emissions (OR = 1.00; CI = 0.73–1.37). Similarly, there was no relation with dairy consumption at any age between birth and 12th grade. These results suggest that height is a risk factor for TGCTs, but the relation is unlikely to be explained by childhood dairy consumption. Because adult height is largely determined in the first two years of life, increased attention to events in this interval might help elucidate the etiology of TGCTs. **(McGlynn KA, Sakoda LC, Rubertone MV, Sesterhenn IA, Lyu C, Graubard BI, Erickson RL. Body size, dairy consumption, puberty, and risk of testicular germ cell tumors. *Am J Epidemiol* 2007;165:355–363)**

VIRUSES

HPV Vaccine and Preexisting Infection

To determine whether vaccination against HPV types 16 and 18 increases the rate of viral clearance in women already infected, data from a phase 3, masked, community-based randomized trial conducted in Costa Rica were used. The study comprised 2,189 women aged 18 to 25 years recruited in 2004 and 2005 who were positive for HPV DNA at enrollment, had at least six months of follow-up, and had follow-up HPV DNA results. Participants were randomly assigned to receive three doses of a bivalent HPV-16/18 L1 protein viruslike particle AS04 candidate vaccine (n = 1,088) or a control hepatitis A vaccine (n = 1,101) over six months. Rates of type-specific viral clearance were compared using generalized estimating equations methods at the 6-month visit (after two doses) and 12-month visit (after three doses). There was no evidence of increased viral clearance at 6 or 12 months in the group that received HPV vaccine compared with the control group. Clearance rates for HPV-16/18 infections at six months were 33.4% (82/248) in the HPV vaccine group and 31.6% (95/298) in the control group (vaccine efficacy for viral clearance = 2.5%; CI = −9.8%–13.5%). HPV-16/18 clearance rates at 12 months were 48.8% (86/177) in the HPV vaccine group and 49.8% (110/220) in the control group (vaccine efficacy for viral clearance = −2.0%; CI = −24.3%–16.3%). There was no evidence of a therapeutic effect for other oncogenic or nononcogenic HPV categories among women receiving all vaccine doses, among women with single infections, or among women stratified by various entry variables. **(Hildesheim A, Herrero R, Wacholder S, Rodriguez AC, Solomon D, Bratti MC, Schiller JT, Gonzalez P, Dubin G, Porras C, Jimenez SE, Lowy DR; Costa Rican HPV Vaccine Trial Group. Effect of human papillomavirus 16/18 L1 viruslike particle vaccine among young women with preexisting infection: A randomized trial. *JAMA* 2007;298:743–753)**

DCEG PEOPLE IN THE NEWS

In April, **Blanche Alter, M.D., M.P.H.,** Clinical Genetics Branch (CGB), spoke on "New insights into Fanconi anemia/breast cancer and dyskeratosis congenita" as part of Hematology Grand Rounds and on "Cancer-prone rare genetic syndromes: How do they instruct us?" as part of Pediatric Grand Rounds at the Mayo Clinic in Rochester, Minnesota. In May, she presented "Predictive markers of myelodysplastic syndrome in the bone marrow of patients with inherited bone marrow failure syndromes" and "Disclosure of 'unwanted' genetic information to benefit a family member" at the Pediatric Academic Societies Annual Meeting in Toronto.

In September, **Parveen Bhatti, Ph.D.,** Radiation Epidemiology Branch (REB), received a DCEG Fellowship Achievement Award.

In July, **Louise A. Brinton, Ph.D.,** Chief of the Hormonal and Reproductive Epidemiology Branch (HREB), gave two presentations on endometriosis and cancer risk at the 23rd Annual Meeting of the European Society of Human Reproduction and Embryology in Lyon, France. Subsequently, Dr. Brinton and **James V. Lacey, Jr., Ph.D.** (HREB), participated in the First Collaborative Group on Epidemiological Studies of Endometrial Cancer meeting in Oxford. Dr. Brinton also served on the steering committee.


Linda Brown

In June, **CAPT Linda Morris Brown, Dr.P.H.,** Biostatistics Branch (BB), was awarded the 2007 Stanley J. Kissel Jr. Award for Outstanding Health Services Professional of the Year at the U.S. Public Health Service Scientific and Training Symposium in Cincinnati.

During May and June, **Nilanjan Chatterjee, Ph.D.** (BB), delivered several presentations. He spoke on "Exploiting interactions for powerful detection of genetic and environmental risk factors for complex diseases" at the Approaches to Complex Pathways in Molecular Epidemiology conference, and he also gave two talks titled "Recent developments in semiparametric methods for analysis of case-control studies in genetic epidemiology" at the International Chinese Statistical Association meeting in Raleigh, North Carolina and at the Western North American Regional Meeting of the International Biometrics Society in Irvine, California.

In June, **Sanford M. Dawsey, M.D.,** Nutritional Epidemiology Branch (NEB), served as a peer reviewer for the Arctic Investigations Program and gave an invited talk on "The role of *H. pylori* in the development of upper gastrointestinal cancers" at CDC in Anchorage.

In May, **Neal D. Freedman, Ph.D., M.P.H.** (NEB), won an NCI Cancer Prevention Research Training Merit Award. The awards are given to the top 10% of cancer prevention fellows for their research excellence, scientific productivity, and service to NCI.

Between April and July, **Mitchell H. Gail, M.D., Ph.D.** (Chief of BB), delivered several presentations: "Absolute risk: Clinical applications and controversies" for the Donna J. Brogan Lecture at Emory University in Atlanta; "A model of absolute invasive breast cancer risk including mammographic density" at the Third International Workshop on Breast Densitometry in San Francisco; "Probability of detecting disease-associated SNPs in case-control genome-wide association studies" and "Absolute risk: Clinical applications and controversies" at the University of California, San Francisco; and "Absolute risk models: Applications and validation" at the Joint Statistical Meetings in Salt Lake City. He also discussed "Resources for understanding cancer risk" on a public teleconference sponsored by the NCI Office of Liaison Activities Conference.

In May, **Mia M. Gaudet, Ph.D.** (HREB), gave two invited talks on "Genetic variation in the estrogen

NEW OFFICE OF EDUCATION ADVISORS

Ann W. Hsing, Ph.D. (HREB), **Mark Purdue, Ph.D.,** Occupational and Environmental Epidemiology Branch (OEEB), and **Sholom Wacholder, Ph.D.** (BB), recently completed three years on the DCEG Office of Education Advisory Group (OEAG). **William F. Anderson, M.D., M.P.H.** (BB), **Amanda J. Cross, Ph.D.** (NEB), and **An-Tsun Huang, Ph.D.** (OEEB), have been appointed as new members. The OEAG deliberates and advises on overall OE programmatic functions, initiatives, and planning. It also implements training-related activities and makes recommendations to the Chief of OE, to the Senior Advisory Group, and to the Division Director. Other members include **Parveen Bhatti, Ph.D.** (REB), **Louise A. Brinton, Ph.D.** (Chief of HREB), **James J. Goedert, M.D.,** Chief of the Viral Epidemiology Branch (VEB), and **Mark H. Greene, M.D.** (Chief of CGB).

metabolism pathway and breast cancer risk" at the Netherlands Cancer Institute in Amsterdam and at the Julius Center, University Medical Center in Utrecht.

In August, **Ethel S. Gilbert, Ph.D.** (REB), spoke on "Estimating cancer risks from exposure to low levels of ionizing radiation" at the Joint Statistical Meetings in Salt Lake City.

In July, **Mark H. Greene, M.D.** (Chief of CGB), presented "Introduction to clinical oncology" at the NCI Summer Curriculum in Cancer Prevention. As part of a two-month Foundation for Advanced Education in the Sciences course on genetics, he also taught "Inherited cancer susceptibility disorders: Gastrointestinal cancers, melanoma, and pediatric syndromes" and "Inherited cancer susceptibility disorders: Rare hereditary cancer syndromes."

In May, **Maureen C. Hatch, Ph.D.** (REB), gave an invited presentation on "Thyroid cancer and non-cancer endpoints in Chornobyl-exposed children" at the Congress of Endocrinology in Kiev, Ukraine.

In April, **Ann W. Hsing, Ph.D.** (HREB), spoke on "Androgens and prostate cancer: What else is new?" at the Keck School of Medicine, University of Southern California. In May, she gave a presentation on "Inflammation and biliary tract cancer" at the NCI workshop on Free Radicals, Oxidative Stress, and Inflammation in Cancer in Bethesda, which was sponsored by the Cancer Redox Biology Faculty and the Cancer Inflammation Program.

In June, **Ruth A. Kleinerman, M.P.H.** (REB), presented "Second cancers in retinoblastoma: What is the risk with modern radiotherapy and no chemotherapy?" at the International Society of Oncology Meeting in Siena, Italy.

In June, **Deukwoo Kwon, Ph.D.** (REB), spoke on "Identifying protein biomarkers from mass spectrometry data with ordinal outcome" at the Center for Computational Biology and Bioinformatics School of Medicine, Indiana University-Purdue University Indianapolis.

During May and June, **Ola Landgren, M.D., Ph.D.,** Genetic Epidemiology Branch (GEB), gave several talks: "Multiple myeloma, chronic lymphocytic leukemia (CLL), and associated precursor diseases" at the NIH-CDC-FDA workshop on Monoclonal B-cell Lymphocytosis and Chronic Lymphocytic Leukemia: Environmental and Genetic Risk Factors in Washington, DC; "Chronic immune stimulation and risk of CLL" at the University of York, United Kingdom; and "Monoclonal gammopathy of undetermined significance: On the pathway to multiple myeloma" at the InterLymph Annual Meeting in Barcelona, Spain.

During July and August, **Sam M. Mbulaiteye, M.D.** (VEB), gave invited talks on "Epidemiological designs to study cancer in HIV-infected populations" at the Annual Meeting of International Epidemiologic Databases to Evaluate AIDS in Sydney, Australia and "Presence but not level of human herpesvirus 8 DNA correlates with Epstein-Barr virus DNA in asymptomatic African children and adults" at the 10th International Workshop on Kaposi's Sarcoma-associated Herpesvirus and Related Agents in Portland, Oregon.

DCEG Linkage received its second consecutive Award of Excellence from the Annual Awards for Publication Excellence (APEX) and an Honorable Mention in the Communicator Awards. APEX is a competition for communications professionals that recognizes excellence in published work; awards are based on the quality of design, editorial content, and the effectiveness and distinction of the publication. The Communicator Awards is an international competition that recognizes superlative work in the communications field. Companies and individuals are judged for talent that exceeds a high standard of excellence and work that is a benchmark for the industry. Managing Editor **Samantha Nhan,** Office of the Director, and the team of reporters, writers, photographers, artists, and editors at DCEG and Palladian Partners are the recipients of these awards.

HEALTH PHYSICS SOCIETY MEETS

In July, five members of REB participated in the Health Physics Society Annual Meeting in Portland, Oregon. **André Bouville, Ph.D.,** gave an invited presentation on the "Assessment of individual doses for use in epidemiological studies"; **Vladimir Drozdovitch, Ph.D.,** spoke on "Radiation measurements made in Belarus during the first few weeks following the Chornobyl accident"; **Kwang Pyo Kim, Ph.D.,** presented a poster on "Occupational radiation dose to cardiologists from cardiac catheterization procedures"; **Dunstana Melo, Ph.D.,** gave a talk on "An 131I biokinetic model with application to hyperthyroid patients"; and **Steven L. Simon, Ph.D.,** delivered "A report from the BiodosEPR-2006 Consensus Committee on biodosimetric methods to evaluate radiation doses at long times after exposure." As an associate editor of *Health Physics*, Dr. Simon also participated in the editorial board meeting.

RADIATION EPIDEMIOLOGY COURSE OFFERED

In May, more than 100 individuals participated in the third offering of DCEG's four-day Radiation Epidemiology Course, according to Course Director **Peter D. Inskip, Sc.D.** (REB). Participants came from across the United States, Brazil, Finland, France, Germany, Japan, and the Netherlands to learn about radiation epidemiology, with a focus on radiation-related cancer.

The first day of the course offered a review of basic radiation physics and dosimetry, radiation chemistry, and radiobiology. The remaining three days highlighted epidemiologic studies of radiation-exposed populations, including atomic bomb survivors in Japan, medically irradiated populations, and groups with occupational or environmental exposures. Methods for quantifying radiation risks, the use of such information in setting radiation protection standards, and risk communication were also discussed. Both ionizing and non-ionizing forms of radiation were addressed. Throughout the course, speakers emphasized the importance of radiation dosimetry in epidemiologic studies, in addition to other key methodologic issues, including challenges in the study of low-dose effects.

The backgrounds and levels of experience among the participants varied. Scientists attended from several federal agencies, including CDC, the Department of Energy, the Food and Drug Administration, and the National Institute of Allergy and Infectious Diseases. A large contingent from the Radiation Effects Research Foundation in Japan also participated.

In addition to Dr. Inskip, REB members who participated included **André Bouville, Ph.D., Ethel S. Gilbert, Ph.D., Maureen C. Hatch, Ph.D., Charles E. Land, Ph.D., Martha S. Linet, M.D., M.P.H., Kiyohiko Mabuchi, M.D., Dr.P.H., Elaine Ron, Ph.D.,** and **Steven L. Simon, Ph.D. Jay H. Lubin, Ph.D.** (BB), and **Margaret A. Tucker, M.D.,** Director of the Human Genetics Program and Chief of GEB, also participated. **Jenna Nober** (REB) served as Course Coordinator. Course information and materials are available at http://radepicourse2007.cancer.gov.

The next course will be offered in 2010.

—Jenna Nober

In May, **June A. Peters, M.S., C.G.C.** (CGB), presented a synopsis of three behavioral studies on "Familial testicular cancer" at the 10th International Meeting on Psychosocial Aspects of Cancer Genetic Testing in Manchester, United Kingdom.

In July, **Philip R. Taylor, M.D., Sc.D.** (GEB), lectured on "Esophageal cancer: Epidemiology and prevention" at the NCI Summer Curriculum in Cancer Prevention.

In May, **Rebecca Troisi, Sc.D.,** Epidemiology and Biostatistics Program, gave an overview of "The diethylstilbestrol story: Health effects in three generations" at the Cancer Registry of Norway in Oslo.

In August, **Margaret A. Tucker, M.D.** (Chief of GEB), was a guest expert on melanoma on New York Public Radio's Leonard Lopate Show.

In May, **Sholom Wacholder, Ph.D.** (BB), gave a talk on "Complex pathways—Opportunities and pitfalls" at the conference on Approaches to Complex Pathways in Molecular Epidemiology held in Albuquerque.

Mary H. Ward, Ph.D. (OEEB), has served on the U.S. Environmental Protection Agency's Board of Scientific Counselors Committee for Evaluation of the National Drinking Water Research Program and on the Institute of Medicine committee, Making Best Use of the Agent Orange Exposure Reconstruction Model, which is a geographic information system–based model for estimating exposures to the herbicide.

GARCIA-CLOSAS TENURED

Montserrat García-Closas

In June, the NIH Central Tenure Committee awarded scientific tenure to **Montserrat García-Closas, M.D., Dr.P.H.** (HREB). After receiving an M.D. from the University of Barcelona Medical School and an M.P.H. and Dr.P.H. from Harvard University, Dr. García-Closas joined the Environmental Epidemiology Branch in 1996 and became a tenure-track investigator in 1999. She has developed multidisciplinary research programs in the molecular epidemiology of ovarian, endometrial, breast, and bladder cancers with an emphasis on genetic susceptibility to the latter two. She has also investigated etiologic heterogeneity of genetic and other risk factors for breast cancer. In addition, Dr. García-Closas has addressed methodological questions relevant to molecular epidemiologic studies and is a founding member of three international consortia. These programs have laid foundations for continuing molecular epidemiology research and advancing the understanding of cancer etiology.

COMINGS . . . GOINGS

Mohamad Al-Rahawan, M.D., a fellow in the Clinical Genetics Branch (CGB), completed a fellowship in pediatric hematology and oncology in May and returned to Syria.


Gabriella Andreotti

In August, **Gabriella Andreotti, Ph.D.,** joined the Occupational and Environmental Epidemiology Branch (OEEB) as a postdoctoral fellow to work with **Michael C.R. Alavanja, Dr.P.H.,** on the effects of pesticides and genes on cancer risk in the Agricultural Health Study. She received a Ph.D. in epidemiology from George Washington University (GWU), where she examined the effects of genes in the lipid metabolism pathway and serum lipid levels on risk of biliary tract cancers and stones under the mentorship of **Ann W. Hsing, Ph.D.,** Hormonal and Reproductive Epidemiology Branch (HREB), and Dr. Paul Levine (GWU). Dr. Andreotti has an M.P.H. in epidemiology from GWU and a B.S. from the University of Maryland, College Park.


Christina Bennett

Christina Bennett, M.S., joined HREB as a Howard Hughes Medical Institute-NIH Research Scholar. She received a B.S. and M.S. from Indiana University, where she is currently a medical student. Under the mentorship of **Allan Hildesheim, Ph.D.,** and **Mahboobeh Safaeian, Ph.D.,** she is evaluating HPV antibody patterns and determinants using data from the HPV-16/18 Vaccine Trial in Costa Rica.


Kelly Bolton

Kelly Bolton joined HREB through the NIH-Cambridge Graduate Partnership Program. She received a B.A. from Cornell University in 2004 and enrolled in an M.D. program at the David Geffen School of Medicine at the University of California, Los Angeles. After two years, she was accepted into the Howard Hughes Medical Institute-NIH Research Scholar program. She spent the last year at the National Human Genome Research Institute, working under the mentorship of Dr. Max Muenke to identify susceptibility genes and gene-environment interactions for attention deficit hyperactivity disorder. At NCI, she is studying genetic susceptibility to breast and ovarian cancers. She divides her time between DCEG, where she is mentored by **Montserrat García-Closas, M.D., Dr.P.H.** (HREB), and the University of Cambridge, United Kingdom, where her mentor is Dr. Paul Pharoah.


Porcia Bradford

Porcia Bradford, M.D., joined the Genetic Epidemiology Branch (GEB) as a fellow. She has a B.S. from the University of Alabama at Birmingham and an M.D. from Duke University Medical School. She completed a one-year fellowship at the NIH Clinical Research Training Program, working primarily in the Surgery Branch of the Center for Cancer Research on immunotherapy for metastatic melanoma and renal cell cancer, and she fulfilled two years of general surgery residency at the Vanderbilt University Medical Center in Nashville. She is currently taking time off from her residency to study the epidemiological aspects of acral lentiginous melanoma, multiple primary melanomas, and familial melanoma with **Alisa M. Goldstein, Ph.D.,** and **Margaret A. Tucker, M.D.** (Director of the Human Genetics Program and Chief of GEB).

Bryan M. Dolan, a postbaccalaureate fellow with the Viral Epidemiology Branch (VEB), has joined Cambridge Associates, a Boston-based firm that works with a number of hospitals, universities, and other nonprofit institutions, as a consulting associate.


Maire Duggan

Maire Duggan, M.D., a senior gynecologic pathologist and professor at the University of Calgary in Canada, has joined HREB for a ten-month sabbatical. She received an M.D. at the University College in Cork, Ireland, and completed her pathology training at Massachusetts General Hospital. She is working with **Mark E. Sherman, M.D.** (HREB), and others across the Division, using her expertise in pathology to improve the histopathologic classification of tumors and perform molecular characterization using tissue microarrays.


Sheri Farasat

Sharifeh (Sheri) Farasat joined GEB as an NIH Clinical Research Training Program Fellow. She recently finished her third year of medical school at the Johns Hopkins University School of Medicine. She graduated from

the University of California, Los Angeles in 2003 with a B.S. in neuroscience and a B.A. in political science. During her yearlong fellowship, she is studying genodermatoses, specifically genotype-phenotype correlations using registry data and families. She is also investigating somatic changes in skin tumors in patients with hereditary leiomyomatosis and renal cell cancer. Her mentor is **Jorge R. Toro, M.D.** (GEB), and her tutor is **Mark H. Greene, M.D.** (Chief of CGB).

Derek Hicks, a program assistant in OEEB, has accepted a position at the U.S. Food and Drug Administration.


Tram Lam

Tram Kim Lam, Ph.D., an NCI Division of Cancer Prevention Fellow, recently joined GEB. She completed her undergraduate studies at Yale University and received an M.P.H. and Ph.D. in epidemiology from the Johns Hopkins Bloomberg School of Public Health. Her research interests include the interplay between genetic variants, infectious agents, and diet in carcinogenesis. She is working with **Maria Teresa Landi, M.D., Ph.D.,** to explore the determinants of lung cancer in the EAGLE (Environment and Genetics in Lung Cancer Etiology) Study.


Jasmine Lew

Quan Lan (Jasmine) Lew, M.S., joined the Nutritional Epidemiology Branch (NEB) as a Howard Hughes Medical Institute-NIH Research Scholar. She received a B.A. and M.S. in neuroscience from Johns Hopkins University in 2004 and completed her third year of medical school at the Pritzker School of Medicine at the

ROBERT BIGGAR RETIRES

In September, **Robert J. Biggar, M.D.,** retired from VEB following an illustrious career studying infectious disease, cancer, and pediatric epidemiology, often in international settings. He grew up in Bahrain and received a B.A. from Pomona College in 1964 and an M.D. from Baylor College of Medicine in 1968. Following an internship in pediatrics at the Baylor Affiliated Hospitals, Dr. Biggar enlisted in the U.S. Navy, in which he served for two years. He completed a pediatrics residency and infectious diseases fellowship at the Los Angeles County Medical Center and was certified by the American Board of Pediatrics in 1974.

Dr. Biggar was an Epidemic Intelligence Service Officer with the U.S. Center for Disease Control from 1973 to 1975. In 1976, he joined the NCI Viral Oncology Program as on-site project officer for the Burkitt Tumor Project in Accra, Ghana. During his four-year stay, Dr. Biggar developed an international reputation for his work on Burkitt lymphoma.

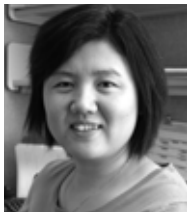
After his return to the United States, he joined NCI's epidemiology program when the HIV/AIDS epidemic was first recognized. Dr. Biggar quickly launched a series of general epidemiologic studies, including a prospective cohort study of homosexual men in Denmark, where sexual contact with Americans was linked to CD4 lymphocyte deficiency. During the ensuing 25 years, he became an international authority on human retroviruses, including HTLV-I and -II and HIV-1. His studies of African and AIDS-associated Kaposi sarcoma (KS) presaged the discovery of the KS-associated herpesvirus, also known as human herpesvirus 8 (HHV-8). Based on field work in the Amazon and collaborations with anthropologists and geneticists, Dr. Biggar characterized the viral archeology of HTLV-II and HHV-8 by identifying pockets of hyperendemicity in isolated Amerindian populations.

Dr. Biggar's clinical trial of birth canal cleansing during childbirth among women in Malawi, 30% of whom were HIV-infected, was particularly important. He found that cleansing with chlorhexidine had no effect on perinatal transmission of HIV, but it significantly reduced postpartum and perinatal morbidity and mortality due to bacterial infections. Dr. Biggar continues to serve on the International Chlorhexidine Working Group to establish intrapartum cleansing as the standard of obstetric care in developing countries.

He has been an exceptional mentor to many young investigators around the world and has received several awards and medals from the Commissioned Corps of the U.S. Public Health Service. Dr. Biggar has relocated to Copenhagen, where he is a senior scientist with the Statens Serum Institute, but he will continue as a special volunteer in VEB.


Joseph Fraumeni, Robert Biggar, and James Goedert.

University of Chicago. She worked in Dr. Harriet DeWitt's laboratory studying the effects of sleep deprivation on impulse control. With **Yikyung Park, Sc.D.,** and **Arthur Schatzkin, M.D., Dr.P.H.** (Chief of NEB), she is investigating diet in relation to cancer using the NIH-AARP Diet and Health Study.


Sharon Liang

Xueying (Sharon) Liang, Ph.D., joined GEB as a Cancer Research Training Award Fellow. She received a Ph.D. in human genetics and an M.S. in applied statistics, both from Vanderbilt University. She also has an M.D. from Tianjin Medical University in China and an M.S. in biochemistry and molecular biology from the Beijing Institute of Radiation Medicine. Her dissertation focused on susceptibility genes for Alzheimer's disease, integrating data from linkage, candidate gene association, and gene expression studies to identify a susceptibility gene on chromosome 10. Under the mentorship of **Lynn R. Goldin, Ph.D.** (GEB), and **Ruth M. Pfeiffer, Ph.D.,** Biostatistics Branch, she is working on linkage and association studies in high-risk cancer families and case-control studies. She is also conducting methodological studies in genetic epidemiology.


Jennifer Loukissas

Jennifer Loukissas, M.P.P., has joined the DCEG Office of the Director as Communications Coordinator. A graduate of Haverford College with a degree in English, she came to NIH in 2002 as a Presidential Management Fellow after completing a graduate degree at Duke University's Terry Sanford Institute of Public Policy. As a fellow, she completed rotations in the NIH Office of the Director, the National Institute on Alcohol Abuse and Alcoholism, the National Institute of Mental Health (NIMH), and the NIH Office of Communications and Public Liaison. She also served as a Health Policy Fellow for the U.S. Senate Committee on Health, Education, Labor, and Pensions. She joined DCEG after working in the NIMH Office of Communications and the NCI Office of Communications and Education.

ROSELYN WEIL RETIRES

In January, **Roselyn (Rusty) Weil** retired from the Epidemiology and Biostatistics Program after 34 years of service at NCI. After graduating from George Washington University, she worked as an elementary school teacher and then as a part-time researcher for a law firm while raising two children. In 1973, she joined Dr. David Byar in NCI's Biometry Branch. Her talents in conducting field studies were recognized, and in 1975, she was transferred to the Epidemiology Branch, where she took on increasing levels of responsibility for the conduct and management of field studies in the Washington, DC metropolitan area. Her professional demeanor, engaging personality, and obsessive attention to detail and documentation enabled her to carry out the entire range of activities required for successful field investigations, from obtaining the cooperation of clinicians and clinical and administrative departments to developing forms, interviewing, writing abstracts, coordinating specimen collection, and quality control. Her success was due not only to her talents but also to her genuine concern for all with whom she worked. She formed long-lasting bonds with clinicians, nurses, record room personnel, and study subjects and their families, always obtaining high study cooperation rates. She has retired to Lititz in Lancaster County, Pennsylvania.

Rajeev Mahajan, M.H.S., a predoctoral fellow in OEEB, has taken a position at the University of Colorado Cancer Center.


Roberto Minutillo

Roberto Minutillo has returned to DCEG as a lead administrative officer in the Administrative Resource Center. During the past seven months, he was a senior administrative officer for the National Institute of Arthritis and Musculoskeletal and Skin Diseases.


Lisa Mirabello

Lisa Mirabello, Ph.D., joined CGB as a postdoctoral fellow. She received a Ph.D. in biomedical sciences with a focus on molecular population genetics at the University at Albany School of Public Health, State University of New York. Her thesis focused on the molecular population genetics of the malaria vector *Anopheles darlingi*. She also has an M.S. in experimental pathology. Her first project in the Division will apply her skills in population genetics and bioinformatics to study genes in telomere biology with her primary mentor, **Sharon A. Savage, M.D.** She is also performing genetic association studies of cancer risk and outcome.

Panagiota Mitrou, M.Sc., Ph.D., left NEB to work as a research associate at the Centre for Nutritional Epidemiology in Cancer Prevention and Survival, a program hosted by the University of Cambridge Department of Public Health and Primary Care.

Chitra Mohla, M.S., left DCEG to take a position in the Office of Health Information Technology Adoption in the Office of the Secretary, U.S. Department of Health and Human Services.


Steven Moore

Steven C. Moore, Ph.D., joined NEB as a postdoctoral fellow. He received an M.P.H. and Ph.D. in cancer epidemiology from Yale University. His dissertation focused on polymorphisms in putative adiposity-related genes as predictors of cancer, and longitudinal assessments of weight and their relationships with specific causes of mortality. Under the mentorship of **Michael F. Leitzmann, M.D., Dr.P.H.,** he is examining physical activity, adiposity, and adiposity-related genes in relation to prostate, breast, endometrial, and renal cancers.


Colleen Pelser

Colleen Pelser joined VEB as a predoctoral fellow. She earned a B.S. in medical and research technology in 2000 from the University of Maryland, Baltimore, where she is a Ph.D. candidate in the Department of Epidemiology and Preventive Medicine. With **James J. Goedert, M.D.** (Chief of VEB), as her mentor, she is focusing on geographic and environmental correlates of classical KS and infection with KS-associated herpesvirus.

Supported by a competitive fellowship from Deutsche Krebshilfe (German Cancer Aid), **Nicolas Wentzensen, M.D.,** has joined HREB. He received


Nicolas Wentzensen

an M.D. in 2000 from the University of Heidelberg School of Medicine, where he will also complete a Ph.D. in applied tumor biology. His dissertation was on the pathogenesis of papillomavirus-associated disease and the evaluation of related biomarkers. He completed a postdoctoral fellowship in the Department of Applied Tumor Biology in the Institute of Pathology at the University of Heidelberg. He is currently completing an M.S. in epidemiology at the University of Mainz. Under the mentorship of **Mark Schiffman, M.D., M.P.H.,** he will be developing and validating biomarkers of precancer and invasive cancer risk.

NEIL PEARCE VISITS DCEG AS DISTINGUISHED LECTURER

Dr. Neil Pearce, Director of the Centre for Public Health Research at Massey University, New Zealand, visited the Division in June as DCEG Distinguished Lecturer in Occupational and Environmental Cancer. Dr. Pearce is a world-renowned expert in the field of occupational epidemiology and epidemiological methods and is also recognized for his contributions to knowledge about the epidemiology of asthma.

During his thought-provoking lecture on "Methodological issues in cancer epidemiology: Ecosystems, populations, cells, and molecules," Dr. Pearce discussed challenges in the field of occupational and environmental epidemiology. He presented the strengths and weaknesses of different "levels of analysis"—ranging from the level of the ecosystem, to populations, to individuals, and to the cellular and molecular levels—using examples from his research on obesity, asbestos, and asthma. He noted that the optimal approach integrates information from all the different levels without collapsing one into the other and that this "multilevel thinking" can be achieved through recognizing the importance of the population context in which exposures occur and adopting a problem-based approach. He underscored the importance of remembering that complexity is the norm rather than the exception and of addressing the major determinants of cancer at the population level through appropriate technology.

During his two-day visit, Dr. Pearce also met with fellows and investigators across the Division and gave a second seminar to members of the Occupational and Environmental Epidemiology Branch on time-related factors in cancer cohort studies.

—Dalsu Baris, M.D., Ph.D.


Neil Pearce (third from left) with DCEG Director Joseph Fraumeni, lecture series sponsor Dalsu Baris, and OEEB Chief Debra Silverman.

NCI DIRECTOR VISITS DCEG

In July, John E. Niederhuber, M.D., NCI Director, visited DCEG for a half-day symposium highlighting the Division's portfolio of projects in breast cancer research. A discussion period followed each of the seven presentations.

The symposium opened with a presentation from **James V. Lacey, Ph.D.,** of the Hormonal and Reproductive Epidemiology Branch (HREB), who presented data from a collaborative study of breast cancer incidence trends in the Kaiser Permanente Northwest health plan database. The analysis, published in an August issue of the *Journal of the National Cancer Institute,* illustrated how the recent decline in breast cancer incidence paralleled the decline in use of postmenopausal estrogen-based hormone therapy.

Next, **Regina G. Ziegler, Ph.D., M.P.H.,** of the Epidemiology and Biostatistics Program, reviewed her recent work on developing new methods of measuring endogenous estrogens and estrogen metabolites. The effort has been challenging due to the complex nature of steroid hormone pathways and existing technology's limited ability to detect low levels of various metabolites. Using state-of-the-art liquid chromatography-mass spectrometry techniques, Dr. Ziegler and her multidisciplinary team designed a novel methodology that reliably and accurately detects 15 different estrogens and estrogen metabolites in blood and urine. Her group is working to extend these techniques to detect androgens, progestagens, and other hormones and to apply them to human tissue samples. Dr. Ziegler described the potential applications of these methods to research on hormonally related cancers.

Stephen J. Chanock, M.D., Director of the NCI Core Genotyping Facility, summarized the Division's work in the NCI Cancer Genetic Markers of Susceptibility (CGEMS) initiative. Starting with genome-wide association studies for prostate and breast cancers, members of the project recently published initial results in *Nature Genetics.* Dr. Chanock highlighted the coordinated replication methodology employed by the CGEMS investigators that maximizes discovery across the entire genome while minimizing the number of false-positive findings.

Montserrat García-Closas, M.D., Dr.P.H. (HREB), and **Rose Yang, Ph.D., M.P.H.,** of the Genetic Epidemiology Branch, presented their work on the heterogeneity of risk factors and genetic associations of breast cancer. Using genomic DNA and tissue samples accompanied by questionnaire and anthropometric data for women in a population-based case-control study, Drs. García-Closas and Yang detected variations in genetic and environmental risk factors by molecular subtypes.

Gretchen L. Gierach, Ph.D., M.P.H. (HREB), discussed the newly established Breast Radiology Evaluation and Study of Tissues (BREAST) project, which Dr. Niederhuber selected to fund with the breast cancer postage stamp proceeds. The project will investigate how breast tissue density and the microenvironment affect breast cancer risk and will identify predictive markers of risk. Participants in the study and its pilot phase are patients in the Vermont Breast Cancer Surveillance System, which is affiliated with the NCI Breast Cancer Surveillance Consortium.

Lastly, **Mark H. Greene, M.D.,** Chief of the Clinical Genetics Branch, provided an overview of various clinical and genetic studies of hereditary breast and ovarian cancer. The Prospective Cohort of *BRCA1/2* Mutation-positive Families, which includes family members with and without *BRCA* mutations, explores candidate gene polymorphisms that might modify *BRCA*-related cancer risk. The Breast Imaging Study examines differences in standard mammographic density and novel breast imaging features (from MRI and digitized mammograms) between mutation carriers and non-carriers. Finally, the Ovarian Cancer Prevention and Early Detection Study (GOG-199) measures the effectiveness of salpingo-oophorectomy in protecting against cancer and evaluates a novel screening strategy (the "ROCA" algorithm) among women prone to ovarian cancer. ■

—Alyssa Minutillo, M.P.H.

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